IORT-containing multimodality treatment for locally advanced primary and locally recurrent rectal cancer

Mannaerts, Guido Hein Huib

IORT-CONTAINING MULTIMODALITY TREATMENT FOR LOCALLY ADVANCED PRIMARY AND LOCALLY RECURRENT RECTAL CANCER

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Promotor:	Prof. Dr. Th. Wiggers
Referenten:	Dr. H.J.T. Rutten Dr. H. Martijn
Beoordelingscommissie:	Prof. Dr. C.J.H. van de Velde Prof. Dr. B.G. Szabo Prof. Dr. P.C. Levendag

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Chapter 1

General introduction, aims and contents of the thesis.

Introduction

Colorectal cancer is the third most common malignancy in The Netherlands and its incidence is rising gradually in the Western world.[1] It is also the second leading cause of cancer death. In The Netherlands every year colorectal cancer is diagnosed in 8,000 patients. About half of these patients will die because of this disease.[2] The highest incidence is found in the sixth and seventh decade and is equally distributed over the sexes.

Rectal cancer is different from cancer of the colon, because rectal cancer has a closer relation to the surrounding structures; is more difficult to resect due to the narrow access to the lesser pelvis; and carries for the aforementioned reason a higher risk for local recurrence (tumor recurrence within the lesser pelvis after treatment). Rectal cancer represents 30% of all new colorectal malignancies.[1]

Seventy-five percent of all rectal cancer patients have a mobile tumor. Radical surgery (negative resection margins) creates the best chance for cure in these patients. Nowadays, these resections are performed according to the Total Mesorectal Excision (TME) technique, which is being accepted as the new standard for the treatment of mobile rectal cancer.[3-5] Basic principle of TME is sharp en bloc resection of the tumor bearing rectal compartment with its mesorectal fat, containing the lymphatic-vascular supply, and its surrounding fascia propria. Success of TME is only warranted if negative circumferential margins (> 2 mm) can be achieved. In that case, these tumors may be called “surgically resectable for cure”, and TME will improve the 5 year survival rate by 20% up to 60-70% and decrease the local pelvic recurrence rate from more than 20% to less than 10%.[6,7]
The remaining patients (25%) present themselves with a rectal cancer extending into or beyond the enveloping fascia propria of the rectal compartment. Subsequently, these tumors have a growth close to or even infiltrating into adjacent structures. TME-surgery alone, will not suffice to realize a radical resection and will result in a high incidence of recurrence of rectal cancer within the small pelvis. Therefore, these tumors can be considered ”surgically non-resectable for cure”.

A local recurrence of rectal cancer constitutes a major problem. It arises in 9-36% of the patients, mostly within 2 to 3 years, after an initial curative resection.[2,7-8] A local recurrent rectal cancer can be considered a separate entity, because it is not confined to one anatomical compartment due to distortion of the anatomical fascial borders as a result of prior surgery. The majority of the patients presenting with a local recurrence are usually treated palliatively. Few patients have a central (anastomotic) pelvic recurrence, without pelvic side wall or sacral involvement, in whom a resection with tumor-free margins can be performed. The high incidence of local re-recurrences observed in patients with pelvic recurrences undergoing radical re-resections is partly explained by the high number of irradical procedures performed due to presacral and/or pelvic sidewall involvement.

Three reasons justify aggressive combined treatment of primary locally advanced and locally recurrent rectal cancer. Firstly, a local recurrence often leads to severely disabling symptoms (i.e., difficult controllable pain, tenesmus, bleeding, ulcerating wounds), which can be palliated temporarily with irradiation, however, for a period lasting no longer than 6-8 months.[9-13] Secondly, nearly 50% of the patients die within two years of local tumor progression without ever developing detectable distant metastases.[13,14] At last, systemic therapy for locally advanced primary or locally recurrent colorectal cancer will not cure the patient and will control local symptoms in few cases.

Pelvic radiation therapy alone results in some extension of survival, however, long-term survival is rare (0-5%).[13,15-19] Furthermore, irradiation provides consistent pain relief in 75 to 100% of patients with symptomatic pelvic recurrences.[13,15,18,20] As already mentioned, this palliative effect lasts for about 6-8 months. Higher doses seem to extend the effect.[13,15,18,19,20] Irradiation doses of 65 Gy to 75 Gy could result in permanent local control.[21] Administration of these high doses, however, is limited by the normal tissue tolerance of the surrounding tissues.[22] Therefore, External Beam RadioTherapy (EBRT) doses are commonly limited to 45-55 Gy (1.8 to 2 Gy fractions).

EBRT at these dose levels can, as a preoperative therapy, be very efficient to reduce the tumor size and viability, and increases the probability for a radical tumor resection.[23,24] After EBRT 50-75% of the primary locally advanced rectal carcinomas become resectable for cure.[25-29] Although resection can be achieved in a great number of these patients, the 5-year incidence of a local recurrence still ranges from 30% to 55%.[14,25,27,28,30-32] The survival rates range from 10% to 26%.[25,30,31] The 5-year local re-recurrence rates and survival rates for locally recurrent rectal cancer after surgery with or without preoperative radiotherapy are, respectively, 37-69% and 7-38%.[8,16,18,19,32-37] The differences in the outcome of these studies can be explained by different inclusion criteria. The ability to perform a radical tumor resection is the only factor that has consistently been shown to have an impact both on overall survival and local control.[14,16,18,38,39]

In conclusion: treatment of primary locally advanced and locally recurrent rectal cancer is frustrated by the fact that a radical resection can often not be achieved, and that the EBRT dose is limited by the normal tissue tolerance. An intraoperatively delivered boost of irradiation can overcome this aforementioned problem. Radiation sensitive dose limiting structures can be displaced from the boost area or be shielded by lead in the boost area. Direct visualization allows confinement of the boost specifically to the area at risk for residual tumor. The biological effectiveness of a single high dose irradiation is considered to be equivalent to two or three times its nominal value in fractionated EBRT form.[40-42] This results in higher effective total local irradiation dose, comparable to EBRT doses up to 100 Gy (50 Gy preoperative EBRT plus 2-3 times 10-20 Gy IORT) with minimal increase of normal tissue toxicity, thus increasing the radiotherapeutic ratio. This boost of IntraOperative RadioTherapy (IORT) can be administered either as IntraOperative Electron beam RadioTherapy (IOERT) or as IntraOperative High Dose Rate brachytherapy (IOHDR).Combining IORT, as a boost to EBRT, and radical surgery with Extended Circumferential Margin Excision (ECME) results in a 15-20% improvement of overall survival,[29,43-45] and a 30% improvement of local control.[29,45] Further improvement of the multimodality treatment could be realized by combining the preoperative EBRT with chemotherapy.

In the Comprehensive Cancer Center South (IKZ) and the Comprehensive Cancer Center Rotterdam (IKR) area surgeons and radiation oncologists have centralized the treatment of patients with unresectable advanced primary rectal cancer and patients with locally recurrent rectal cancer, in order to develop a uniform IORT-containing multimodality treatment with curative intent. This treatment combines high dose with preoperative EBRT, radical ECME-surgery and IORT. Preoperative EBRT has recently been combined with chemotherapy.
All patients with locally advanced primary rectal cancer (with extension into the surrounding structures) or a locally recurrent rectal cancer, and without distant metastases, were candidates for this combined treatment.

Aim of the study

Main goal of the present study was to evaluate the role of IORT-containing multimodality treatment in the treatment of locally advanced primary and locally recurrent rectal cancer. Several aspects were studied:

- The outcome in terms of survival, disease free survival and local control, of IORT-containing multimodality treatment (i.e., preoperative EBRT, ECME and IORT) for locally advanced primary or locally recurrent rectal carcinoma was analysed and compared with the results obtained in historical control groups, with the same tumor characteristics, treated by conventional treatment modalities (i.e., radiotherapy-only or combined radiotherapy plus surgery).
- Abdominosacral resection of the tumor, being an important surgical technique to facilitate access to the small pelvis and to obtain tumor-free margins in the multimodality treatment protocol for locally advanced primary and locally recurrent rectal cancer, was analysed in relation to the surgical anatomy of the small pelvis and with regard to the obtained results.
- The anesthetic management of the operation: i.e., dealing with massive transfusion requirements, hypothermia, intraoperative changes, intraoperative transport and remote monitoring during IORT, was described and the perioperative results were analysed.
- The treatment-related urogenitial morbidity induced by this IORT-containing multimodality treatment for locally advanced primary or locally recurrent rectal cancer was analysed.

Subsequent chapter distribution

Chapter two describes the value of IOERT-containing multimodality treatment in locally advanced primary rectal cancer. In *Chapter three,* the value of IORT-containing multimodality treatment in locally recurrent rectal cancer is compared with historical control groups from the Catharina Hospital Eindhoven and the Daniel den Hoed Cancer Center Rotterdam, with the same tumor characteristics but treated with conventional treatment modalities: i.e., irradiation only or preoperative irradiation and by surgery. *Chapter four* analyses the results of IOERT-containing multimodality treatment in locally recurrent rectal cancer. *Chapter five* reports on the surgical technique and results of the abdominosacral approach used in the resections of rectal cancer with growth adherent to the sacrum or lateral pelvic wall and used to obtain a larger access to perform a radical resection. In *Chapter six*, the anesthetic management and results are described.
Chapter seven describes the urological complications and the late urogenital morbidity caused by this multimodality treatment. *Chapter eight* summarizes the results and general conclusions of this study.

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Chapter 2

Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery and IOERT in locally advanced primary rectal cancer.

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Guido H.H. Mannaerts, M.D.*, Hendrik Martijn, M.D., Ph.D.‡, Mariad A. Crommelin, M.D.‡, Wim Dries, M.Sc.♦, Ocker J. Repelaer van Driel, M.D., Ph.D.§, and Harm J.T. Rutten, M.D., Ph.D., F.R.C.S.*

Catharina Hospital, Departments of Surgery *, Radiotherapy ‡, and Physics ♦, Eindhoven, The Netherlands.

Chairman, Colo-Rectal Tumor Group CCCS (Comprehensive Cancer Center South area) §, The Netherlands.

Introduction

Clinically fixed primary rectal cancers involve the circumferential fascial borders of the mesorectum. Dissection through the tumor is frequent; therefore, resection can be considered palliative and almost synonymous with local recurrence.
Preoperative external beam radiation therapy (EBRT) has a downsizing and downstaging effect, which improves the probability of a complete resection. However, even after preoperative irradiation, many patients still have positive resection margins resulting in an overall local recurrence rate between 30% to 55%,[1-6] and a poor overall survival rate between 10% to 26%.[3,5,6] Necessary tumorcidal doses are above 60 Gy and cannot be delivered without exceeding normal tissue tolerance of the surrounding organs.[7-9]
In view of dose delivery limitations of EBRT, intraoperative electron beam radiation therapy (IOERT) administered as a boost after preoperative EBRT, specifically to the area at risk, can increase the therapeutic ratio by improving tumor control without significantly increasing the normal tissue toxicity.[10-16]
Since 1994, surgeons and radiotherapists of the Comprehensive Cancer Centre South in The Netherlands have developed an aggressive multimodality treatment protocol using the potentially increased therapeutic ratio of preoperative EBRT with IOERT boosting and extensive pelvic surgery, aiming at complete tumor resection.
This report analyses the results of this multimodality treatment protocol in patients with locally advanced primary rectal cancer without apparent distant metastases.

Methods and materials

Patients (Table 1)

From October 1994 to July 1999, 48 patients with primary locally advanced rectal adenocarcinoma were scheduled for the multimodality treatment. At the resection laparotomy, 10 patients did not receive IOERT and were excluded from further analysis. Six of them had extrapelvic disease, and a palliative resection of the primary tumor was performed in 2 of them. One patient was excluded due to unresectability. The remaining 3 had very wide margins, and it was not possible to define an area at risk for the IOERT boost.

The mean age of the eligible 38 patients was 64 years (range 33-82 years) and the male/female-ratio was 22/16. All patients had fixed tumors. The inferior border of all tumors was below the promontory. The distance from the anal verge to the inferior margin of the tumor was 0-5 cm in 16 patients, 6-10 cm in 14 patients, and > 10 cm in 8 patients. CT-scan or MRI failed to show an interface between tumor and surrounding structures in 10 patients (26%) and did show definite infiltration into surrounding structures in 28 patients (74%). The CT-scan or MRI revealed enlarged lymph nodes in 15 patients (39%). Symptoms were classified as: no symptoms (n = 1, 3%), symptoms without pain (n = 27, 71%) and symptoms with pain (n = 10, 26%).[17]

Table 1. **Patient categories after preoperative EBRT**

	No.	(%)
Patients explored	48	
No resection / No IOERT		
Locally unresectable	1	(2)
Multiple intraabdominal metastases	4	(9)
Resection		
Resection without IOERT		
No adherence	3	(6)
Multiple intraabdominal metastases	2	(4)
Resection with IOERT		
No detectable metastases	38	(79)
Total number of eligible patients	38	
Age (years)		
Mean	64	
Range	33-82	
Sex		
Male	22	(58)
Female	16	(42)

Methods

All patients had a CT scan or MRI, to provide details on the location and the degree of invasion of the fixed primary rectal tumor. A liver ultrasound and a plain chest X-ray were used to exclude disseminated disease. Referring surgeons were encouraged to perform a staging laparotomy to exclude extrapelvic disease and to prepare the patient for EBRT. The cranial extent of the tumor was marked by clips, a stomy was constructed, and a spacer was placed in the pelvis to keep the small bowel out of the EBRT field. A biological spacer, i.e., the omentum or the distal sigmoid, was preferred and if not possible an artificial spacer (breast prosthesis) was used instead. The constructed stomy was a left-sided permanent colostomy if an abdomino-perineal resection was expected, or a right-sided diverting colostomy or ileostomy if restoration of bowel continuity appeared to be possible. During the staging laparotomy, the tumor was not mobilized to avoid tumor spill.

All patients received preoperative EBRT, which was delivered by a three-field technique, with one posterior and two lateral portals. The pelvic field borders were as follows: *lateral*, 1-1.5 cm lateral to the inner bony pelvis; *superior*, the promontory (L5-S1); *inferior*, below the obturator foramina or the perineum if the carcinoma was located in the lower one/third of the rectum (4-5 cm below the tumor); *dorsal*, posterior to the sacrum; and *ventral*, wide margin anterior to the target volume as determined by CT-scan.[18] If there was clinical evidence of involvement of the bladder, the prostate, the cervix or uterus, not only the internal iliac nodes but also the external iliac nodes were included in the radiation field. In such case the anterior border of the lateral field was positioned along the upper border of the pelvic bone.

A dose of 50.4 Gy in 1.8 Gy fractions, 5 fractions per week, was delivered with 10 MV photons using an isocentric technique. Following the ICRU recommendations, the dose was prescribed to the isocenter and the doses within the target volume ranged from 95% to 107%.[19] Some referred patients had received a dose different to the standard 50.4 Gy. (Table 2.)
In 1999 the protocol was changed, and chemotherapy was added to the EBRT. An intravenous bolus of 350 mg/m^2 5-FU in combination with Leucovorin 20 mg/m^2 was administered one hour before each irradiation in week one and five of the EBRT.

In order to allow downsizing of the tumor, resection with IOERT was scheduled 4-6 weeks after completion of the EBRT. Perioperatively, the abdomen was checked for liver and extra-pelvic peritoneal disease and resection was not performed in those patients found to have extrapelvic metastases. First, if present, the rectosigmoid was transected well above the pelvic entrance to improve exposure and to facilitate the development of the postero-lateral plane. Downward dissection was performed according to the TME-principles, however, if the tumor had infiltrated beyond the proper fascia, an extended circumferential margin excision (ECME) was done. The selected type of resection depended on the tumor infiltration in three major planes: i.e., the *anterior plane*, which is bordered by the bladder and the internal genital organs; the *lateral plane*, with the ureters, internal iliac vessels and branches crossing through the suspensory webs and the intrapelvic part of the obturator internus muscle; and the *posterior* and *postero-lateral plane*, which is in close relation to the levator ani muscles, the intrapelvic attachment of the piriformis muscle, the sacral nerve and vascular plexus, and the sacrum. In case of involvement of ventral structures an exenterative procedure was performed and in case of postero-lateral wall involvement an abdominosacral resection was done. A low anterior resection was only considered in tumors with at least 5 cm distance from the anal verge. The tumor status of the circumferential margin was verified by frozen sections taken from the areas considered to be at risk. Anastomoses after low anterior resection were protected by right-sided diverting colostomies or ileostomies. An omentoplasty was performed to protect the anastomosis or to fill an empty pelvic space.

IOERT was performed within a dedicated IOERT radiation suite with an Elekta SL-25 linear accelerator and an in-house developed fixed applicator system. The accuracy of dose delivery with this system is within a range of ± 5%. The applicator diameter was chosen in such a way that it covered the area at risk within a margin of ± 1 cm; bolus material was used, if necessary, to ensure sufficient surface dose. The outcome of the frozen sections determined the IOERT dose. If negative, 10 Gy was administered, and when positive with microscopic residual disease or gross residual disease (less than 2 cm^2) 15 Gy was applied, and when positive with gross residual disease (more than 2 cm^2), 17.5 Gy was delivered. Guidance for these dosages was protocol 88-20 of the Radiation Therapy Oncology Group.[20] The IOERT dose was specified on the 90% isodose along the central beam axis. The depth of potential tumor involvement of the area at risk was estimated to select the energy needed to obtain an isodose of 90% ±1 cm beyond this tumor depth. The energies being used ranged from 6-18 MeV, corresponding to an isodose depth of 1.4 to 2.8 cm depending on the diameter of the applicator (5-9 cm), bevel end of the applicator ($15\text{-}30^0$), the need of bolus material, and the angle between applicator and surface to be irradiated. Normally, IOERT was delivered through an abdominal access. However, the prostate could only be irradiated transperineally.

The completeness of the resection was based upon the final examination of the specimen by the pathologist and was considered complete if the margins were negative. A local recurrence was defined as a relapse within the EBRT-field, and an in-field recurrence was defined as a recidivism within the IOERT-field. Local pelvic control, DFS and survival curves were calculated from the date of resection plus IOERT until the last follow-up, using the actuarial method of Kaplan-Meier and curve comparison for discrete variables was performed with the log Rank test and Chi-Square test.

Results

EBRT, Surgery and IOERT (Table 2)

All patients received EBRT and 82% received 50.4 Gy (range 25 Gy to 61 Gy). Six patients received preoperative radiochemotherapy.

Four different surgical procedures were performed: 12 low anterior resections (31%), 14 abdomino-perineal resections (37%), 6 abdomino-transsacral resections (16%), and 6 pelvic exenterations (16%). The resected adjacent organs were: bladder plus prostate (n = 3), uterus plus top of the bladder (n = 1), uterus plus dorsal vagina (n = 2), and dorsal vagina only (n = 2). Two patients had a resection of a nonfunctional kidney due to tumor obstruction of the ureter. Bowel continuity could be restored in 15 patients (39%).

Frozen sections were not taken in 7 of the 38 patients because the resection was thought to be complete, and consequently, 10 Gy IOERT was administered. This later revealed to be incorrect in one.

Final pathology showed in 31 (82%) patients' negative resection margins. IOERT dose 10 Gy was delivered in all but one, who received 15 Gy dose because frozen sections were false-positive. Four patients had microscopically positive margins and had received 15 Gy (n = 2), 10 Gy (n = 1), and 12.5 Gy (n = 1) IOERT dose, respectively. Non-radical resections with gross tumor residue were performed in 3 patients who had received 17.5 Gy (n = 2) and 15 Gy (n = 1), respectively. Seven patients (18%) received IOERT trough a perineal access: 4 at the lateral pelvic wall and 3 at the prostate. One patient had 2 separate nonoverlapping fields of IOERT application.

The sensitivity of the peroperative frozen sections in 31 patients was 83%, the specificity 96% and the accuracy 94%.

The average operation time, including anaesthesia time, was 345 min (5 hours and 45 minutes) with a range of 120-560 minutes. The average blood loss was 2.5 litre (range 0.5-8.0) with an average of 2.0 litre packed cells (range 0-17L) transfused.

Table 2. **Diagnostic and treatment characteristics**

	No.	(%)
Radicality resection		
Negative margins	31	(82)
Microscopically positive margins	4	(10)
Macroscopically positive margins	3	(8)
Pathological tumor stage		
No growth beyond proper fascia	22	(58)
Growth into surrounding structures	16	(42)
Lymph node metastases	13	(34)
• Lymph nodes on CT/ MRI	*7*	*(54)*
• Lymph nodes not on CT/ MRI	*6*	*(46)*
Symptoms		
No symptoms	1	(3)
Symptoms without pain	27	(71)
Symptoms with pain	10	(26)
Distance inf. tumor margin to anal verge		
0-5 cm	16	(42)
6-10 cm	14	(37)
11-20 cm	8	(21)
Local growth on CT-scan/ MRI		
Extension to other structures	10	(26)
Growth into surrounding structures	28	(74)
Pathological lymph nodes	15	(39)
Total dose EBRT (Gy)		
25	2	(5)
35	1	(3)
44	1	(3)
45	1	(3)
47	1	(3)
50.4	31	(82)
61	1	(3)
Surgical procedure		
Low anterior resection	12	(31)
Abdomino-perineal resection	14	(37)
Abdomino-transsacral resection	6	(16)
Pelvic exenteration	6	(16)
Sphincter apparatus postop.		
Intact	15	(39)
Resected	23	(61)
Viscera resection		
Dorsal vagina	4	(10)
Uterus	3	(8)
Bladder and prostate	3	(8)
Bladder top	1	(3)
Kidney	2	(5)
Frozen sections		
Positive	6	(16)
Negative	25	(66)
Not taken	7	(18)

Table 2. **Diagnostic and treatment characteristics** (continued)

	No.	(%)
IOERT fields		
Single	37	(97)
Double	1	(3)
Total dosage IOERT (Gy)		
10	32	(82)
12.5	1	(3)
15	4	(10)
17.5	2	(5)
IOERT energies (MeV)		
6	4	(10)
8	15	(38)
10	13	(33)
12	3	(8)
15	3	(8)
18	1	(3)
IOERT applicator diameter (cm)		
5	8	(20)
6	21	(54)
7	7	(18)
8	1	(3)
9	2	(5)
IOERT applicator bevels (degrees)		
15	4	(10)
30	35	(90)

Final pathology demonstrated no tumor extension beyond the mesorectal fascia in 20 patients (53%) and infiltration into the surrounding structures in 16 patients (42%) . In two patients (5%), no residual tumor could be found in the resected specimen on histological examination. In 5 patients only few viable tumorcells could be found in the specimen and in another 5 patients extensive superficial tumor necrosis and fibrotic reaction due to the preoperative irradiation was observed. Four of them had received radiochemotherapy. In 13 patients (34%) lymph node metastases were present. Seven of the 13 had preoperative suspected nodes on CT-scan/ MRI.
Infiltration depth or presence of lymph node metastases did not interfere with the ability to perform complete resections.

Patterns of failure/ Survival

After a mean follow-up of 21 months (range 1-57 months) five patients (13%) were documented with a local failure: 3 IOERT infield recurrences and 2 within the external beam volume. Two of these 5 patients had positive margins with gross residual disease (EBRT/ IOERT: 25/ 15 Gy and 50.4/ 17.5 Gy), 1 microscopically positive (EBRT/ IOERT: 50.4/ 15 Gy) and 2 patients had negative resection margins (EBRT/ IOERT: both 50.4/ 10 Gy). The overall 3-year local control rate (LCR), distant control rate (DCR), disease free survival (DFS), and survival (S) were, respectively, 82%, 68%, 65% and 72%.

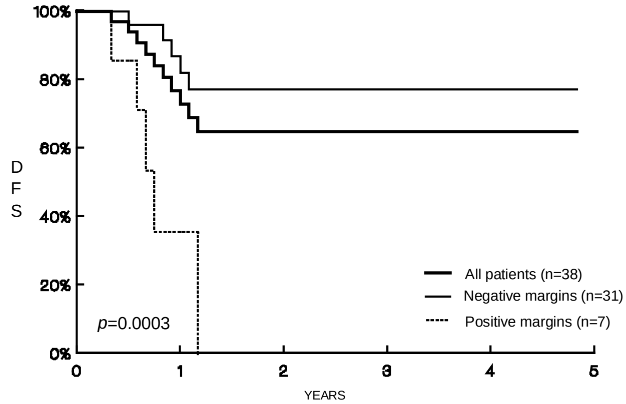

Figure 1. Kaplan-Meier disease free survival (DFS) curves by the radicality of resection (positive vs. negative).

Completeness of resection had a significant influence on DFS (negative vs. positive margin, $p = 0.0003$) and distant control rate (negative vs. positive margin, $p = 0.002$) (Fig. 1 and 2). There was a trend towards better local control after resection with negative margins in comparison with positive circumferential margins ($p = 0.19$) (Fig. 3).

Depth of infiltration did not influence local control, DFS and survival. The presence of lymph node metastases resulted in a significant higher metastases rate ($p = 0.03$) and a trend towards a worse DFS ($p = 0.09$). The presence of preoperative pain correlated with a less favourable DFS ($p = 0.008$) and metastases rate ($p = 0.001$) (Fig. 4).

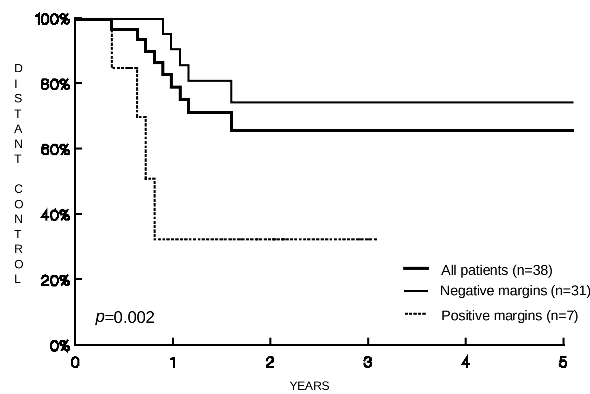

Figure 2. Kaplan-Meier distant control curves by radicality of resection (positive vs. negative)

Complications (Table 3)

In one patient, radiochemotherapy was abandoned at a dose of 35 Gy due to severe diarrhea. Peroperatively, one accidental ureteral injury occurred and no perioperative deaths occurred.

Postoperative complications were observed in 20 (53%) patients. Temporary urinary retention (n = 7), venous thrombosis of the leg (n = 2), and wound infections (n = 9) could be treated conservatively. Reinterventions for postoperative complications were needed in 7 patients: two ileostomies for anastomotic dehiscence, one correction of an abdominal fascia dehiscence, one closure of a perforated duodenal ulcer, one revision of a colostomy, one haemostasis of a postoperative bleeding and one drainage of a wound abscess. The median hospital stay was 15 days (range 7-118).

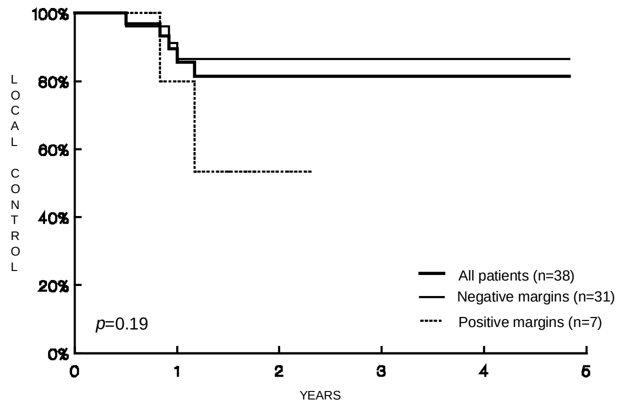

Figure 3. Kaplan-Meier local control curves by radicality of resection (positive vs. negative).

Table 3. **Complications**

	No.	(%)
Preoperative EBRT		
Abandon EBRT due to diarrhea	1	(3)
Peroperative		
Ureteral injury	1	(3)
Postoperative		
Wound infections	11	(29)
Urinary retention	7	(18)
Venous thrombosis of the leg	2	(5)
Anastomotic dehiscence	2	(5)
Abdominal fascia dehiscence	1	(3)
Perforated duodenal ulcer	1	(3)
Dysfunction of colostomy	1	(3)
Bleeding in pelvic region	1	(3)
Late postoperative		
Death of other causes		
Death due to malaises	2	(5)
Death due to sepsis	1	(3)
Lower extremity neuropathy	3	(8)
Sepsis	1	(3)

Late postoperative complications were observed in 6 patients. Two elderly patients died 6 months postoperatively as a result of an overall depression causing total malaise, but without any signs of recurrence. Another patient died five months postoperatively due to sepsis after drainage of a presacral abscess also without any signs of recurrence. Three patients (8%), all without preoperative plexopathic symptoms, developed grade I neuropathy,[21] which was temporarily in 2. The IOERT dose in these patients was 10 Gy.

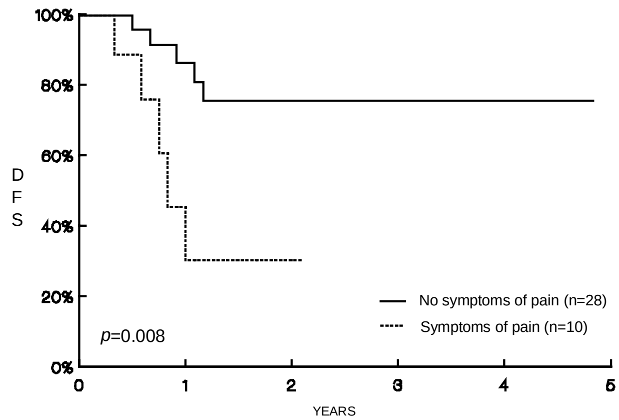

Figure 4. Kaplan-Meier disease free survival (DFS) curves by symptoms of pain vs. no-pain

The daily life pattern was affected in 3 of the currently living 30 patients, due to tiredness (n = 2) and overall loss of muscular strength (n = 1) (Table 4.). All eight patients who worked preoperatively could restart their job. The observed urinary tract complications were: complete incontinence (n = 1), partial continence (high frequency, some leakage); n = 2) and hesitation of urination (n = 7).

Discussion

In locally advanced primary rectal cancers with extension to other structures or ingrowth into other structures the chance of an incomplete resection at the circumferential margins is considerable. Extensive resections with extended circumferential margin excision (ECME), especially in cases with involvement of the lateral or posterior pelvic wall, are necessary to achieve a complete resection. If tumor residue is left behind, recurrences in most cases develop within 2 years and will interfere with the quality of life for the remaining of the patient's life.[12]

Preoperative EBRT has distinct advantages as opposed to postoperative EBRT, i.e., reduction of tumor size, improvement of resectability, alteration of implantability of tumor cells that may be disseminated during an incomplete resection, detection of patients with metastases detected at the restaging workup or laparotomy, and reduction of treatment interval between EBRT and IORT.[17,22]

After EBRT, 50% to 75% of the tumors become amenable for complete surgical resection,[2,4,5,23-26] and as much as 75% to 89% become resectable.[13,27,28] Although resection can be achieved in most of the patients after EBRT, the 5-year incidence of a local recurrence still remains in the range of 30% to 55% with subsequent survival ranges from 10% to 26%.[1-6] Even after apparently complete resection, local failure rate is in the range of 30% to 55%.[29] Several studies have shown that local control is dose-dependent and should exceed 60 Gy.[30,31] However, small bowel toxicity prevents such high doses of EBRT.[8] In view of tissue tolerance, an EBRT dose of 50 Gy is considered to be optimal.[15,16]

Table 4. **Current status survivors**

	No.	(%)
Total survivors at moment of analysis	30	(79)
Daily life pattern		
Undisturbed	27	(90)
Disturbed	3	(10)
Work		
Working before operation	8	(27)
Restarted	8	(100)
Abandoned	0	(0)
Urinary incontinence	3	(10)

An additional boost delivered during the operation by means of intraoperative electron beam radiotherapy can overcome these dose-limitations. The advantages of IOERT are that the radiation dose can be applied very specifically to the area at risk, under direct visual control and with the possibility of shielding or mobilizing the surrounding dose-limiting structures out of the radiation field. The depth of the 90% isodose can be varied by selecting the energy (MeV). A single IOERT boost dose is biologically equivalent to 2 or 3 times its nominal value in the fractionated form.[32,33] Thus in combination with EBRT, equivalent doses of 70 to 80 Gy can be achieved, with the potential of sterilizing microscopic tumor residue. The result appears to be most effective in patients undergoing complete resection.[34] Improvement of local control rate in the approximately level of 30% and overall survival with 15% to 20% have been reported by combining IOERT as a boost to EBRT.[10,35-37] Nerve tissue is the most important dose-limiting factor to be considered. Kinsella found a linear relationship between IOERT dose and time to onset of limb paresis.[38] An IOERT dose of 12.5 Gy is considered to be the cut off point for IOERT induced neuropathy.[12]

This study shows an overall 3-year local control rate (LCR), DFS and survival (S) rate of 82%, 65%, and 72%, respectively (Fig. 1, 2 and 3). These results are comparable to the figures presented by other institutions using the same multimodality approach (LCR 70%-85%, DFS 45%-48% and S 51%-60%).[12-15,39-42] Because follow-up is relatively short, survival is less meaningful than local control and DFS. After resections with negative circumferential margins, a significant better DFS ($p = 0.0003$)

and a lower metastases rate (p = 0.002) were observed in comparison with positive margins patients.
Remarkably, infiltration depth was of no prognostic significance in this multimodality treatment. This indicates that extending the circumferential margin and performing a more complete resection successfully counterbalanced the deeper invasion of more progressive tumors. Presence of lymph node metastases seems to be related to a poorer outcome.

Neuropathic pain caused by infiltration of the plexus was a significant factor for DFS and metastasis rate. This is in concordance with Suzuki, although reporting on locally recurrent rectal cancer.[17]

The downstaging effect of preoperative radio(chemo)therapy has been identified by others.[43-49] In this study 12 patients with a tumor growing beyond the proper fascia were downstaged within this border. In 2 patients no viable, and in 5 only few viable, tumor cells were observed. In 8 of the 15 patients with pathological lymph nodes on the preoperative imaging, no malignant lymph nodes were found.

Extensive local growth was only in one of the patients a reason to aboard the procedure. A complete resection was obtained in 31 of the 38 patients (82%).

None of the patients developed ARDS or MOF despite average large volumes of blood loss. Rapid intraoperative blood transfusions to prevent hypotension and anemia were thought to be crucial. There were no perioperative deaths, similar to other IOERT studies.[15,37]

The relative high incidence (53%) of complications is considered to be acceptable in the light of the extent of the operation necessary to obtain complete resections. Moreover, most were transient. Wound infection, which was the most frequent complication (n = 11), caused prolonged hospitalisation or long-term management in only 4 patients. The complication rate in this study is comparable with the 51.5% of Eble but is lower then the 84% complication rate published by Huber.[14,50] The 8% neuropathy rate (n = 3) is comparable to the 10% reported by Willett, but is lower than the 32% described by Gunderson.[12,15] In 2 of the 3 patients the neuropathy was temporary.

Future perspectives

Further improvement may be realized by combining the preoperative EBRT with preoperative chemotherapy. Memorial Sloan Kettering investigators compared the results of preoperative EBRT with or without chemotherapy in patients with fixed tumors, which resulted in a higher complete response rate (20% vs. 6%) and a lower incidence of positive nodes (30% vs. 53%).[27,28] Furthermore, the resectability rate increases from 64% to 90% with radiochemotherapy compared to patients receiving radiation therapy alone. Similar findings are reported by Frykholm and Shumate.[51,52] Adding chemotherapy may also address the problem of systemic failure that has an incidence higher than 50%.[11] Schild reported an improved survival rate from 44% to 51% when using radiochemotherapy.[53] Eble found a 4-year actuarial overall survival and relapse-free survival of 97% and 82% after radiochemotherapy and IOERT versus 81% and 59%, respectively, after EBRT and IOERT ($p = 0.01$).[50] The improvement of the results can be explained by improved local control due to the radiation sensitization effect of concomitant chemotherapy and the systemic effects of the chemotherapy. In our study 4 out of 6 patients treated with radiochemotherapy showed a remarkable downstaging. Radiochemotherapy, as well as adjuvant postoperative chemotherapy, has been incorporated in our new multimodality treatment protocol.

Conclusions

Although this is a retrospective study, the obtained results seem to indicate that multimodality treatment is feasible and promotes high local disease control rates and with a potential positive effect on survival in patients with locally advanced primary rectal cancer.

Preoperative EBRT followed by extended resections to obtain a free circumferential margin resulted in a high rate of curative resections. IOERT is essential to eliminate tumor residue that may be left behind. Centralization of these patients was a prerequisite for the development of this multimodality treatment.

Development of metastatic disease in more than 50% of the patients still is a major oncologic problem. Preoperative concomitant radiochemotherapy and postoperative adjuvant chemotherapy have to be investigated in future protocols.

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Chapter 3

Comparison of IORT-containing multimodality treatment to historical modalities for locally recurrent rectal cancer.

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Guido H.H. Mannaerts, M.D.*, Harm J.T. Rutten, M.D., Ph.D., F.R.C.S.*,
Hendrik Martijn, M.D., Ph.D.‡, Patrick E.J. Hanssens, M.D.♦,
Theo Wiggers, M.D., Ph.D., F.R.C.S. §.

Catharina Hospital, Departments of Surgery * and Radiotherapy ‡,
Eindhoven, The Netherlands.

University Hospital Rotterdam/ Daniel den Hoed Cancer Center,
Departments of Radiotherapy ♦ and Surgical Oncology §, Rotterdam,
The Netherlands.

Introduction

Local recurrence of rectal cancer following radical surgery is observed in 3-35% of patients and occurs in 67% to 93% of these patients within two years after the primary resection.[1-7] In the absence of a treatment for local recurrence, a median life expectancy of 4 to 7 months has been reported.[8-11] One-fourth up to half of the patients die of disease confined to the pelvis.[1,8,12-16] Most of these patients will die after prolonged suffering from severe pain, barely assuaged by large doses of analgetics. Their course may be complicated by rectal bleeding, ulcerating perineal lesions, tenesmi, mucus discharge, ureter or bowel occlusion, severe edema in the lower extremities and enterocutaneous fistulas.

Many efforts have been undertaken to prevent such disasters by improving the surgical technique in primary resectable disease.[4,17-19] Less attention has been paid to the treatment for those with a local recurrence.
Conventional therapeutical options for locally recurrent rectal cancer are limited and the results are poor.[20,21] Most institutions treat these patients with a palliative intent, with either irradiation or surgery, often considering this as the only possible option.
The fact that local recurrences have a major negative impact on the patient's quality of life, and the fact that a large percentage of these patients outlive the palliative effect of irradiation or surgery alone and ultimately die of local tumor progression, justify an aggressive multimodality treatment to improve local palliation and to provide permanent cure in some patients.

This study describes the historical development of a multimodality treatment strategy at the Catharina Hospital in Eindhoven and the Daniel den Hoed Cancer Center in Rotterdam. Within the last decades, the treatment has developed from a palliative treatment with irradiation, to combined EBRT and surgery, and finally to preoperative EBRT and extensive surgery combined with intraoperative radiotherapy (IORT).

This study compares the results of these three different types of treatment for locally recurrent rectal cancer that were subsequently applied in the two institutions.

Patients and methods

Since many years a close collaboration exists between the Catharina Hospital in Eindhoven and the Daniel den Hoed Cancer Center in Rotterdam. In this retrospective analysis, three major treatment protocols for locally recurrent rectal cancer are distinguished. Based upon the treatment protocols three patient groups with the same patient characteristics were compared. None of the patients had received irradiation in the past and all patients were without detectable distant metastases at the time of treatment for the local recurrence.

Table 1. **Patient and treatment characteristics**

	1	2	3
Total number of patients	94	19	33
Patient characteristics			
Age (years)			
Mean	67	62	63
Range	42-88	49-73	39-84
Sex			
Male	47	12	22
Female	47	7	11
Treatment primary tumor			
Surgery			
Low anterior resection	49	14	24
Abdomino-perineal resection	45	5	9
Initial TNM-stage			
T1	5	2	2
T2	12	4	7
T3	76	11	24
T4	1	2	-
N0	57	8	24
N+	37	11	9
Time between primary resection and local recurrence (months)			
Mean	18	19	21
Range	6-109	4-54	3-92
Staging of local recurrence Suzuki-Gunderson system [22]			
F0	-	7	7
F1	-	5	11
F2	-	6	12
F3	-	1	3
Wanebo system [23]			
Tr1-2	-	0	0
Tr3	-	7	12
Tr4	-	9	12
Tr5	-	3	9
Treatment local recurrence			
EBRT dose (Gy)			
Median	50	50	50
Range	12-80	32-65	25-50.4
Surgery			
Low anterior res.	-	5	5
Abdomino-perineal res.	-	10	15
Exenteration	-	4	6
Abdomino-sacral resection	-	-	7
Completeness of resection			
Microscopical negative margins	-	7	21
Microscopical positive margins	-	8	7
Macroscopical positive margins	-	4	5
IORT			
10 Gy IOERT	-	-	11
15 Gy IOERT	-	-	6
17.5 Gy IOERT	-	-	3
10 Gy IOHDR	-	-	13

1=EBRT-only, 2=Combined EBRT-Surgery
3=IORT-Multimodality treatment

Patient and primary treatment characteristics are described in table 1. Staging was performed according to the system suggested by Suzuki and Gunderson,[22] as well as by the system proposed by Wanebo (table 2).[23]

1) From May 1975 to December 1990, 94 patients were treated with EBRT only at the Catharina Hospital and the Daniel den Hoed Cancer Center. The percentage of low anterior resections (LAR) as the primary resection was 52% and the percentage of T3+4 tumors was 82%, with 39% having positive lymph nodes. The median time between the primary tumor resection and the local recurrence was 18 months (range 6-109 mo).

Insufficient number of CT-scans were available to classify the degree of local tumor progression.

EBRT doses ranged from 32-80 Gy (median 50 Gy), in 1.8-2 Gy fractions/ 5 times a week.

Table 2. **Staging systems for locally recurrent rectal cancer**
Suzuki-Gunderson classification [22]

F_0	No, site (or confined to perineum/ small bowel)
F_1	One site
F_2	Two sites
F_3	Three or more sites

Discerning: the anterior site (anterior adjacent organs), the left and right lateral site (lateral pelvic walls) and the posterior site (sacrum or coccyx)

Wanebo classification [23]

$T_{R1\text{-}2}$	Invasion in bowel wall (subserosal)
T_{R3}	Invasion in perirectal fat
T_{R4}	Invasion in anterior urogenital organs
T_{R5}	Invasion in sacrum or pelvic side walls

2) From October 1989 to December 1996, 19 patients were treated with combined preoperative irradiation followed by resection at the Daniel den Hoed Cancer Center. The percentage of LAR as the primary resection was 74% and the percentage of T3+4 tumors was 68%, with 58% having positive lymph nodes. The median time between the primary tumor resection and the local recurrence was 19 months (range 4-54 mo).

The degree of local tumor progression was scored: F0 (n=7), F1 (n=5), F2 (n=6) and F3 (n=1) and Tr1-2 (n=0), Tr3 (n=7), Tr4 (n=9) and Tr5 (n=3).

EBRT doses ranged from 32 - 65 Gy (median 50 Gy), in 1.8-2 Gy fractions/ 5 times a week. Five low anterior resections (26%), 10 abdominoperineal resections (53%) and 4 pelvic exenterations (21%) were performed. The resection margins were negative in 7 patients (37%), microscopically positive in 8 (42%) and macroscopically positive in 4 patients (21%).

3) From February 1994 to September 1999, 20 patients were treated with preoperative EBRT followed by resection and intraoperative electron beam radiotherapy (IOERT) at the Catharina Hospital, and from 1997 to 1999, 13 patients were treated with EBRT followed by resection and intraoperative high dose rate brachy therapy (IOHDR) in the Daniel den Hoed Cancer Center. The percentage of LAR as the primary resection was 73% and the percentage of T3+4 tumors was 73%, with 27% having positive lymph nodes. The median time between the primary tumor resection and the local recurrence was 21 months (range 3-92 mo).

The only preoperative exclusion criteria for IORT-multimodality treatment were detectable distant metastases or infiltration in vertebra S2 or higher. Six other patients had been excluded during the resection because of intraabdominal metastases (n=4), irresectability (n=1) and wide radical resection without a discernible area at risk indicated for IORT-boosting (n=1).

The stages of the local recurrences of the included 33 patients were scored: F0 (n=7), F1 (n=11), F2 (n=12) and F3 (n=3) and Tr1-2 (n=0), Tr3 (n=12), Tr4 (n=12), and Tr5 (n=9).

EBRT doses ranged from 25-50.4 Gy (median 50 Gy), in 1.8-2 Gy fractions/ 5 times a week (n=28) or 5 x 5Gy fractions (n=5). The three most recent patients received concurrent chemotherapy with 5-FU and Leucovorin as an IV-bolus for five consecutive days during the first and last week of radiation therapy. The resection types consisted of a LAR in 5 patients (15%), an APR in 15 (46%), a pelvic exenteration in 6 (18%) and an abdomino-sacral resection (ASR) in 7 patients (21%). The resection margins were negative in 21 patients (64%), microscopically positive in 7 (21%) and macroscopically positive in 5 patients (15%).
Twenty patients from the Catharina Hospital received IOERT. Frozen sections, taken to assess the radicality of the resection, determined the IOERT dosage according to the RTOG protocol: microscopically negative margins 10 Gy, microscopically positive margins 15 Gy and positive margins with gross residual disease (more than 2 square cm tumor residue) 17.5 Gy.[24] Doses were 10 Gy (n=11), 15 Gy (n=6) and 17.5 Gy (n=3). Thirteen patients from the Daniel den Hoed Cancer Center received IOHDR. IOHDR was performed with a flexible intraoperative template (FIT) and with an Iridium-192 source. A dose of 10 Gy was prescribed at 1 cm depth. The target volume was defined as the area at risk for microscopic disease with 1 cm margin.[25-27] The minimal follow-up of the 33 patients was 12 months.

The final assessment of the radicality of the resection was made by the pathologist. A resection was considered complete if the distal and circumferential margins were free of tumor, even if they were close. A local recurrence or failure was defined as tumor regrowth within the lesser pelvis. Local control and disease free survival curves were calculated using the actuarial method of Kaplan-Meier. Comparisons between curves for discrete variables were performed with the Log-Rank test and Chi-Squared test.

Results

Group 1. (EBRT-only)

None of the investigated variables showed significant difference between the patients receiving EBRT at the Catharina Hospital (n=48) and the patients receiving EBRT at the Daniel den Hoed Cancer Center (n=46). Therefore, both groups were analysed as one. The overall survival (S), disease free survival (DFS) and local control (LC) rates at 3-year were: 14%, 8% and 10%, and at 5-year: 6%, 7% and 8% respectively. The median local symptom free period was 5 months (range 0-70 months). The median survival was 18 months (range 2 - 120).

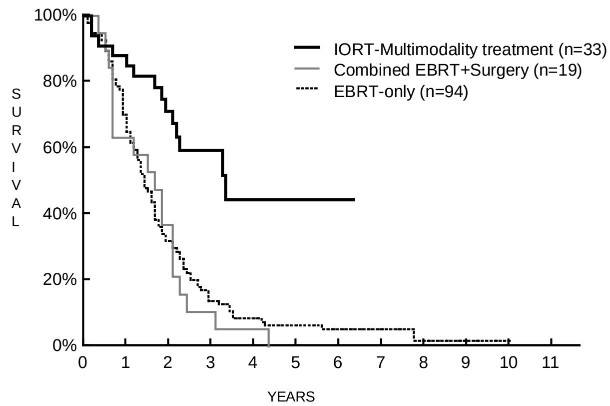

Figure 1. Survival comparing EBRT-only vs combined EBRT-surgery vs IORT-multimodality treatment (EBRT-only *vs* IORT-multimodality treatment: p=0.00001, combined EBRT-surgery *vs* IORT-multimodality treatment: p=0.0001).

Group 2. (Combined EBRT- surgery)

The overall 3-year S, DFS and LC rates were 11%, 0% and 14%. Patients with a negative resection margins (n=7) had a 3-year S, DFS and LC rate of respectively 29%, 0% and 29%. Patients with positive resection margins (n=12) had a disappointing 3-year S, DFS and LC rate of 0%, 0% and 0% respectively. The status of the resection margin was significant for survival (p=0.04), but not for DFS and LC. The median survival after treatment of the local recurrence was 19 months (range 3 - 52 months).

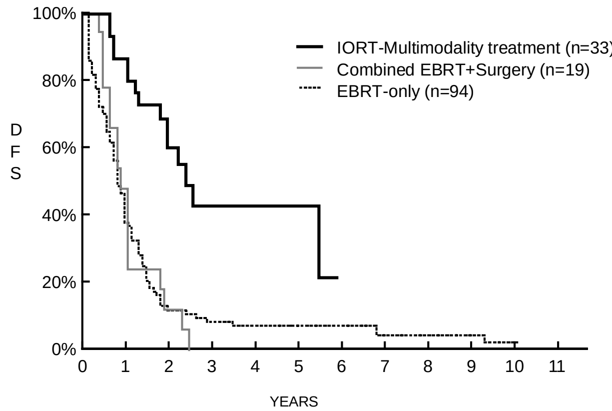

Figure 2. Disease free survival comparing EBRT-only *vs* combined EBRT-surgery vs IORT-multimodality treatment (EBRT-only *vs* IORT-multimodality treatment: p=0.00000, combined EBRT-surgery *vs* IORT-multimodality treatment: p=0.00001).

Group 3. (IORT-multimodality treatment)

None of the investigated variables showed significant difference between the Daniel den Hoed Cancer Center IOHDR-group and the Catharina Hospital IOERT-group. Therefore, both modalities were analysed as one group.

The overall 3-year S, DFS and LC rates were 60%, 43% and 73%. Patients with negative resection margins (n=21) had a 3-year S, DFS and LC rate of 63%, 62% and 89% respectively. In contrast, patients with positive resection margins (n=12) had 3-year S, DFS and LC rates of respectively 52%, 0% and 45%. These differences were significant for LC (p=0.048) and DFS (p=0.04).

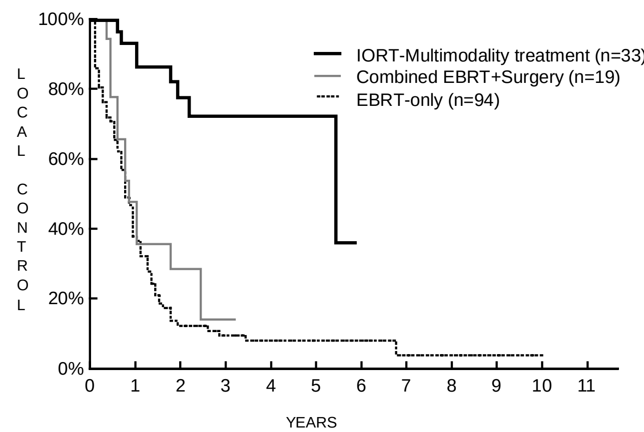

Figure 3. Local control comparing EBRT-only *vs* combined EBRT-surgery vs IORT-multimodality treatment (EBRT-only *vs* IORT-multimodality treatment: p=0.00000, combined EBRT-surgery *vs* IORT-multimodality treatment: p=0.00005).

All five patients who were excluded from the protocol due to intraabdominal metastases (n=4) and irresectability (n=1) died after a mean survival of 11 months. The other patient with wide radical margins who received no IORT, has no evidence of disease after a follow-up of 17 months.

Comparison of the treatment groups

No significant differences in S, DFS and LC were observed between the EBRT-only group and the combined EBRT-surgery group.

The IORT-multimodality treatment group showed a significant better S, DFS and LC compared to the EBRT-only and the combined EBRT-surgery groups (p<0.001).

A possible bias may be introduced by surgeons' growing experience. This is reflected by the fact that negative margins were realized in 7 out of 19 patients of the EBRT-surgery group compared to 21 out of 33 patients in the IORT-multimodality treatment group. In view of this, stratification for status of the margin seems justifiable. If only resections with negative resection margins were considered a better S, DFS and LC were observed in the IORT-multimodality treatment group in comparison to the combined EBRT-surgery group (resp.; p=0.049, p=0.001, p=0.0004). Comparison of patients with positive resection margins revealed a significant survival (p=0.001), DFS (p=0.02)and LC (p=0.03) benefit for the IORT group as well.

Two patients (11%) of the combined EBRT-surgery group died as a result of the treatment. One after 3 months due to pelvic necrosis and infection and the other due to severe kidney dysfunction caused by post-renal obstruction 6 months postoperatively. Another eight patients (42%) developed a perineal infection. Neuropathy grade I, according to the RTOG and EORTC toxity criteria,[28] was observed in three patients (16%) postoperatively.

In the IORT-multimodality treatment group three patients (9%) died as a result of treatment related complications: one patient had several pelvic bleedings, which necessitated repeated reinterventions, subsequently ARDS resulted in death one month postoperatively; another patient also died one month postoperatively due to abdominal sepsis as a result of anastomotic dehiscence; the third patient died 3 months postoperatively of the sequelae of pelvic necrosis. Five other patients (15%) developed a perineal infection, which needed reoperation in one. Neuropathy, grade I (n=3) and grade II (n=1), was observed in 12% of the patients.

Discussion

The 5-year survival rate of 6% of the EBRT-only group compares to published data in other studies.[20,29-31] Analysis of dose-response relationships indicates that improved palliation, local control and survival can be achieved with increasing radiation doses.[20,29,31,32]

Due to the absence of the visceral rectal fascia, which has been removed or distorted during the primary resection, the tumor compartment of the recurrence is not well defined and can encompass any pelvic structure. Therefore, even after aggressive surgery positive resection margins are common, leading to high local recurrence rates (55-77%) and subsequent poor survival figures (20-30%).[3,33-42]

As a more aggressive surgical therapy generally is not feasible, much emphasis is placed on the use of adjuvant external beam radiation therapy. Preoperative radiation therapy can reduce the tumor mass, increasing the likelihood of obtaining a resection with negative margins, and alters the implantability of tumor cells that may disseminate during an incomplete resection.[43] Again, even after preoperative EBRT, resection margins often still are positive in locally recurrent tumors, resulting in high overall local recurrence rates of 39-62% and poor survival rate of 10-25%.[2,7,22,33,34,44-46]

In the combined treatment group of this study, in which 12 patients (63%) had a positive resection margin, corresponding poor overall 3-year S (11%), DFS (0%) and LC (14%) were observed.

The response to irradiation correlates with dose, and doses in excess of 60 - 70 Gy are required to achieve sterilisation.[20,31,32,47] These doses go beyond the normal tissue toxicity level.[45,48] A preoperative EBRT dose of 50 Gy in previously non-irradiated patients and a dose of 30 Gy in previously irradiated patients is considered to be optimal.[48,49]

Addition of IORT, applied as a boost to the area at risk for residual tumor, can overcome the problem of dose-limitation and potentially can improve the therapeutic ratio. A single high radiation dose is considered to have the biological effectiveness of two to three times the equivalent fractionated EBRT dose.[50,51] Radiosensitive normal structures, such as small bowel, ureter, and bladder, can, in many cases, be mobilized out of the IORT-radiation field or shielded from the radiation by the use of lead.[22,52]

In this study IORT was applied in 33 patients. The overall 3-year S, DFS and LC were respectively 60%, 43% and 73%. This survival, DFS and local control were significantly better than the results achieved with EBRT-only or with combined EBRT-surgery. The comparability of the patient groups can be questioned, as patient selection bias exists. The EBRT-only group may contain different tumors than the resected patients groups. However, the only exclusion criteria for resection was local tumor extension into vertebra S2 or higher. The majority of EBRT-only patients would have undergone resection if they would have presented nowadays. The combined EBRT-surgery and the IORT-multimodality treatment group had the same rate of primary abdominoperineal resections (26% vs 27%), a comparable interval between primary surgery and the local recurrence (19 mo vs 21 mo) and the same percentage of T3+4 tumors at the primary T-stage (68% vs 73%). The number of positive nodes differed markedly (58% vs 27%). This can be an explanation for the worse survival and disease free survival of the combined EBRT-surgery group, but not for the local control rates.[53]
The IORT-multimodality treatment group had somewhat higher scores of local progression in comparison with the EBRT-surgery group. As these groups were

comparable the increased number of complete tumor resections must be due to improved surgical skill, rather than patient selection. Introduction of abdominosacral resections in the IORT-multimodality treatment group (21%) illustrates the more extended and demanding surgical approach.

The results of this study compare favourably to the data presented in other IORT-multimodality treatment studies, that report an overall 3-year survival rate of 31-56%,[22,45,54-57] a DFS rate of 19-33%,[22,44,57,58] and a local control rate of 30-75%.[22,45,54,55] The high rate of negative margin resections (64%) in this study, is an important factor influencing the outcome.[52] Other studies have reported improved local control and survival with addition of IORT to preoperative EBRT and extended resection, however, prospective randomized trails do not exist.[22,59]

Mortality (9%) and morbidity of the resected patients in line with reported figures.[34,35] Wound sequelae (18%), neuropathy (12%) and urogenital morbidity (40-50%) were frequently observed.[60]

Concomitant chemotherapy is reported to enhance the preoperative radiotherapeutic effect, resulting in a higher resectability rate and improved survival in locally advanced primary rectal cancer.[61-65] Therefore, radiochemotherapy has been incorporated in the IORT-treatment protocol, since the beginning of 1999.

Postoperative chemotherapy is not a standard procedure in The Netherlands. However, systemic failure in more than 50% of patients treated successfully for their locally recurrent rectal cancer with IORT-multimodality treatment, remains a serious problem.[66] Therefore, adjuvant postoperative chemotherapy will be explored in future studies.

Conclusion

At the Catharina Hospital in Eindhoven and the Daniel den Hoed Cancer Center in Rotterdam, the outcome of treatment for locally recurrent rectal cancer has changed. Two elements of the present treatment protocol appear to be responsible for a better result: 1, an increase of the therapeutic ratio of the radiotherapy by combining preoperative radiotherapy with IORT, and 2, optimalization of surgery aiming at complete resection with negative margins. The absence of the visceral rectal fascia and the enlargement of the tumor volume and subsequent surgical compartment are the anatomical basis for the extended surgical approach.

The willingness of referring surgeons to centralize the treatment of patients with locally recurrent rectal cancer was a prerequisite to develop this approach. Centralization of these patients permits increasing surgical experience, that is held responsible for the decrease of positive margin resections. Despite these possible selection biases and the improved surgical skill over the years, results are at least favouring IORT.

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Chapter 4

Intraoperative electron beam radiation therapy for locally recurrent rectal carcinoma.

Int J Radiat Oncol Biol Phys 1999; 45: 297-308.

Guido H.H. Mannaerts, M.D.*, Hendrik Martijn, M.D., Ph.D.‡,
Mariad A. Crommelin, M.D.‡, Guido N.M. Stultiëns, M.D.*,
Wim Dries, M.Sc.□, Ocker J. Repelaer van Driel, M.D., Ph.D.§, and
Harm J.T. Rutten, M.D., Ph.D., F.R.C.S.*

Catharina Hospital, Departments of Surgery *, Radiotherapy ‡, and
Physics □, Eindhoven, The Netherlands.

Chairman, Colo-Rectal Tumor Group CCCS (Comprehensive Cancer
Center South area) §, The Netherlands.

Introduction

After an apparently curative resection for rectal cancer, local recurrences develop in a high percentage, ranging from less than 10% to 50%, depending on stage of disease and surgical technique.[1-4] Unresected or palliatively resected, local recurrences carry a poor prognosis, with a mean survival ranging from 7 to 12 months.[5-9] Many patients will die of disabling local disease, with perineal ulceration, chronic pelvic pain, or rectal bleeding. Ureteral obstruction or subsequent urinary sepsis also threatens them. Many patients never develop systemic disease.[10]

Sometimes, "re-resections" can be curative: i.e., in cases of pure anastomotic recurrences after low anterior resection,[11-13] or isolated perineal recurrences without pelvic sidewall or sacrum involvement.[9,14] However, in the absence of fascial borders, which have been severed during surgery for the primary rectal cancer, local recurrences commonly present with fixation to surrounding organs or structures. If surgery is considered an option, more radical surgical procedures are required, although margins of resection will often be positive, and these recurrences are palliatively extirpable, but surgically nonresectable for cure.[15-17]

Radiation therapy alone results in pain relief in 70% to 100% of patients with local recurrences and transient local disease stabilization for half a year, but has a curability rate of less than 5% and most patients will die within 2-3 years.[7,18-23] Even if external beam radiation therapy (EBRT) is combined with resection, aiming at R0-resection, a high local recurrence rate of 39-62% and a poor survival rate of 10-25% is reported, despite the fact of favorable patient selection.[2,15,16,21,24-29] Radiation dose should exceed 60 Gy for microscopic residual disease and even higher to reach a tumorcidal dose for macroscopic tumor.[19,22,30,31] However, small bowel toxicity limits the delivery of a higher dose of EBRT.[15] So it seems that conventional treatment strategies for locally recurrent rectal cancer are frustrated by the fact that usually a radical resection can not be performed and that the EBRT dose is limited by normal tissue tolerance. Intraoperative electron beam radiation therapy (IOERT) directed specifically to the resection area at risk for tumor persistence may help to overcome this problem.

In 1994, surgeons and radiotherapists of the Comprehensive Cancer Centre South developed an aggressive combined treatment of preoperative EBRT, surgical re-resection, aiming at R0-resection, or at least R1-resection, through extended circumferential margin excision (ECME), and IOERT with the intention to cure or at least to improve long lasting palliation. This analysis was made to determine the outcome of this multimodality treatment in patients with locally recurrent rectal cancer without distant metastases.

Methods and materials

Patients *(Tables 1 and 2)*

From February 1994 to September 1998, 51 patients, without apparent distant metastases or with only a resectable solitary metastasis, were scheduled for combined resection and IOERT. Ten patients did not receive IOERT. Despite preoperative screening, six appeared to have intraabdominal metastases at the definitive laparotomy and subsequently no resection was performed. Three had an irresectable local recurrence and in only one of these a palliative resection was performed. In one patient IOERT was not delivered, because the ureter was in the area at risk, a radical resection had been performed, and he was suspected to have lung metastasis. The remaining 41 had both a resection and IOERT. Four of them had a resection of a solitary distant metastasis perioperatively (liver, n = 2; lung, n = 1; and coecum, n = 1) and were excluded from the following analysis.
The remaining 37 patients (18 men and 19 women) had a mean age of 60 (range 41-84 years).

Table 1. **Patient categories after preoperative EBRT**

	No.	(%)
Patients explored	51	
No resection		
Locally unresectable	2	(4)
Multiple intra-abdominal metastases	6	(12)
Resection		
Resection without IOERT		
No adherence	1	(2)
Locally unresectable	1	(2)
Resection with IOERT		
Solitary metastasis	4	(8)
No detectable metastases	**37**	(72)

The initial primary tumor was located in the rectum in 26 patients, in the rectosigmoid in 11 patients. The primary resections consisted of 19 low anterior resections, 10 abdominoperineal resections, one local procedure, and seven rectosigmoid resections of which one was extended to an exenterative procedure. Thirty patients (81%) had their first local recurrence, four (11%) their second, two (5%) their third, and one (3%) his fourth recurrence. Twenty-four patients (65%) had a preserved sphincter-apparatus before the current resection. In the past, 20 patients (54%) had received irradiation with usual fraction size of 2 Gy (13 patients: 50 Gy/ 25 fractions).

Table 2. **Patient characteristics**

	No.	(%)
Total number	37	
Age (years)		
Mean	60	
Range	41-84	
Sex		
Male	18	(49)
Female	19	(51)
Number of local recurrences (LR)		
First LR	30	(81)
Second LR	4	(11)
Third LR	2	(5)
Fourth LR	1	(3)
Surgery (primary)		
Low anterior resection	19	(51)
Abdominoperineal resection	10	(27)
Local procedure	1	(3)
Rectosigmoid resection	7	(19)
Sphincter apparatus preoperative		
Intact sphincter apparatus	24	(65)
Prior sphincter app. resection	13	(35)
Previous EBRT		
EBRT	20	(54)
No EBRT	17	(46)
Symptoms		
Asymptomatic	6	(16)
Symptomatic	12	(32)
Symptomatic and pain	19	(52)
Central	*24*	*(65)*
Peripheral	*13*	*(35)*
Time to recurrence (months)		
Median	28	
Range	13-104	

The remaining seven patients had received a variety of total doses and fraction sizes (2: 25 Gy/5Fx; 1: 36 Gy/18Fx; 1: 46 Gy/23Fx; 1: 25 Gy/5Fx + 30 Gy/15Fx; 1: 56 Gy/28Fx; 1: 60 Gy/30Fx) and one chemotherapy. The median interval between the initial treatment and the current local recurrence was 28 months (range 13-104 months).

Methods *(Table 3)*

If complaints and/or physical examination raised suspicion of a local recurrence, a multiplane high-resolution MRI was made to image the local recurrence, and if so, to ascertain the location and extent of the recurrence. The extent of the tumor on MRI was classified as central location (n = 4), extension to adjacent structures (n = 15), true infiltration into neighboring organs or pelvic structures (n = 18). An endoscopic biopsy or a needle biopsy was taken to prove malignancy. This biopsy could be taken in 36 patients (positive n = 32, suspicious n = 3, negative n = 1). Further staging was performed by liver ultrasound and chest radiography. Asymptomatic recurrences (n = 6) were discovered by regular endoscopic follow-up (n = 2), elevated carcinogenic embryonal antigen (CEA) levels (n = 3), and coincidentally at a laparotomy for a hysterectomy (n = 1).

A staging laparotomy was part of the preoperative procedures to exclude extrapelvic disease and to prepare the patient for preoperative EBRT by clipping the cranial level of the tumor, placing a spacer, and constructing a stoma if necessary. The spacer was placed to displace small bowels as much as possible out of the small pelvis. A biological spacer like the omentum or the distal sigmoid was preferred and if not feasible an artificial spacer (mamma prosthesis) was used instead.

The patients with no previous history of pelvic irradiation (n = 17) received a full course of 50.4 Gy (n = 15) preoperative radiation (1.8 Gy per fraction, 5 fractions per week) with a linear accelerator (10 MV photons). One referred patient had received 60 Gy and in another patient EBRT was abandoned at 16 Gy due to an ileus. At the start of the present study, patients who had received radiation therapy as part of their initial treatment (n = 20), did not receive EBRT as part of their treatment for this recurrence (n = 15). However, in the last period of the study, previously irradiated patients (n = 5) received, prior to the resection, 30 Gy in 2-Gy fractions, which was well tolerated.

EBRT was delivered by a three-field technique, utilizing one posterior and two lateral portals.[32] The pelvic field borders were: the lateral borders extending 1-1.5 cm lateral of the bony pelvis, the cranial border being the promontory (L5-S1), the caudal border was below the foramina obturatoria. The dorsal border encompassed the sacrum, and the anterior border was chosen in such a way that the initial tumor region be widely covered. If the local recurrence was low-seated, the perineum was included in the radiation volume.

In two cases, referred by another radiotherapy center, concurrent chemotherapy was administered with 5-flourouracil (5-FU) regimens as an intravenous bolus for 5 consecutive days during the first and the last week of radiation therapy.

Surgical exploration followed 4-6 weeks after completion of EBRT. At the start of the laparotomy, the abdomen was carefully checked for liver, nodal, or peritoneal metastases. For each individual case the selected type of surgery was based upon the area of fixation delineated by the MRI scan.

Four quadrants can be discerned: anterior, both lateral and dorsolateral quadrants, requiring a different approach to perform a R0-resection. Furthermore, two different levels along the pelvic axis, supra- and infrapiriform, pose different surgical problems. Suprapiriform lateral recurrences will, contrary to infrapiriform, involve the sacral nerve plexus. Any attempt to resect and irradiate most likely will result in nerve damage. At any level or in any quadrant, the realization of a radical resection necessitates resection with extended free circumferential margins. Generally, four types of ECME could be identified: a) Pelvic floor level or posterolateral infrapiriform level involvement was treated by abdominotranssacral or abdominotranscoccygeal resection. b) Anterior involvement was treated by pelvic exenteration; bladder and prostate resection in men and (dorsal) vagina and/or uterus extirpation in women. c) Lateral wall involvement was approached by abdominoperineal resection with ECME or if necessary by abdominotranssacral resection in cases where a wider access was needed. d) Central local recurrences were treated by a low anterior resection or an abdominoperineal resection with ECME. The extended lateral margins could involve the ureter, vascular or nerve structures. The type of resections in this group of 37 patients consisted of 3 low anterior resections (8%), 12 abdominoperineal rectum resections (33%), 15 abdominotranssacral resections (40%), in case of infiltration into or fixation to the sacrum, and 7 pelvic exenterations (19%), if infiltration into female or male genital organs or the bladder existed. The resected adjacent organs were: bladder and prostate (n = 3), uterus (n = 7), vagina (n = 5), of which three partial, and adnexa (n = 2). A Bricker bladder reconstruction was performed in three patients.
At the end of the operation an omentoplasty was performed to fill the empty pelvic space or to protect the anastomosis.

During surgery, frozen sections were taken to assess the radicality of the resection. The outcome of the frozen sections determined the IOERT dosage: radical (R0) resection: 10 Gy; microscopic residual disease (R1): 15 Gy; more than 2 square cm tumor residue (R2): 17.5 Gy. Guidance for these dosages was protocol 88-20 of the Radiation Therapy Oncology Group.[33] The IOERT dosages were specified on the 90% isodose along the central beam axis. The depth of potential tumor involvement of the area at risk was estimated to select the energy needed to obtain an isodose of 90% radiation depth ±1 cm beyond this tumor depth. The energies being used had a range of 6-18 MeV, corresponding to an isodose depth of 1.4 to 2.8 cm depending on the diameter of the applicator, bevel of the applicator, the need of bolus material, and the angle between applicator and surface to be irradiated. IOERT was performed with an Elekta SL-25 linear accelerator and an in-house developed, fixed applicator system. The accuracy of dose delivery with this system is approximately 5%. The applicator diameter was chosen in such a way that it covered the area at risk within a margin of ±1 cm; bolus material was used, if necessary, to ensure sufficient surface dose. Normally, IOERT was delivered through the abdomen. However, in two cases with very distally seated tumor residue the perineal approach was used.

Anamnestic symptoms were analyzed in order to investigate if they could reveal preoperative selection criteria for this aggressive treatment strategy. The symptoms of a local recurrence vary with its location and extent into the surrounding structures. Several findings reflect a more central location: i.e., anal blood or slime loss, change of defecation patterns, fecal obstruction, or absence of symptoms, and several signs predict a more peripheral location: i.e., diffuse pelvic pain caused by plexus infiltration, persisting perineal fistulas, ureter obstruction, or ileus.[34] The symptoms of the local recurrences were classified as central in 24 patients (65%) or peripheral in 13 patients (35%). In this study, six patients (16%) were asymptomatic, 12 patients (32%) symptomatic, and 19 patients (52%) symptomatic with pain.[21]

Definitions. The pathologist based the conclusive judgment for radicality of resection in this study upon the examination of the specimen. A resection was considered radical if the margins were free of tumor even when the margins were close.

A local recurrence or failure was defined as tumor regrowth within the EBRT field, and an infield recurrence was defined as a recurrence within the IOERT field. Local recurrence and distant metastases were scored until the patient's death. However, they were censored for disease free survival (DFS) when the first site of failure was detected. Salvage resections after renewed local failure were censored and therefore remained to affect local control (LC) rate.

Patients with preoperative (n = 2) or peroperative (n = 2) solitary metastasis were not included, since other IOERT studies do not include these patients and otherwise a comparison could not be made.

LC and DFS curves were calculated using the actuarial method of Kaplan-Meier. Comparisons between curves for discrete variables were performed with the log-rank test, chi-squared test, and Fisher exact test. An outcome of $p < 0.05$ was considered statistically significant.

Results

Surgery and IOERT (Table 3)

Peroperative frozen sections were not taken in 5 patients (14%) because wide free circumferential margins were considered to be obtained and subsequently 10 Gy IOERT was administered. Final pathology also confirmed that margins were not involved. Twelve patients (32%) had negative frozen sections and final pathology showed two were false-negative (R1). All false-negative cases had received only 10 Gy irradiation. Twenty patients (54%) had (true) positive frozen sections, of which six appeared microscopically irradical (R1) and 14 macroscopically irradical (R2).

Table 3. **Diagnostic and treatment characteristics**

	No.	(%)

Local growth MRI		
Central	4	(11)
Adjacent/ tethered	15	(40)
Infiltration/fixed	18	(49)
Biopsy		
Positive	32	(86)
Suspicious	3	(8)
Negative	1	(3)
Not performed	1	(3)
Total dose EBRT (Gy)		
0	15	(40)
16	1	(3)
30	5	(14)
50	15	(40)
60	1	(3)
Surgical procedure		
Low anterior resection	3	(8)
Abdominoperineal resection	12	(33)
Abdominotranssacral resection	15	(40)
Pelvic exenteration	7	(19)
Radicality resection		
Radical (R0)	15	(40)
Microscopic irradical (R1)	8	(22)
Macroscopic irradical (R2)	14	(38)
Viscera resection		
Vagina	5	(14)
Uterus	7	(19)
Adnex	2	(5)
Bladder and prostate	3	(8)
Frozen sections		
Positive	20	(54)
Negative	12	(32)
Not taken	5	(14)
Total dosage IOERT (Gy)		
10	15	(40)
15	12	(33)
17.5	10	(27)
IOERT fields		
Single	32	(86)
Double	5	(14)

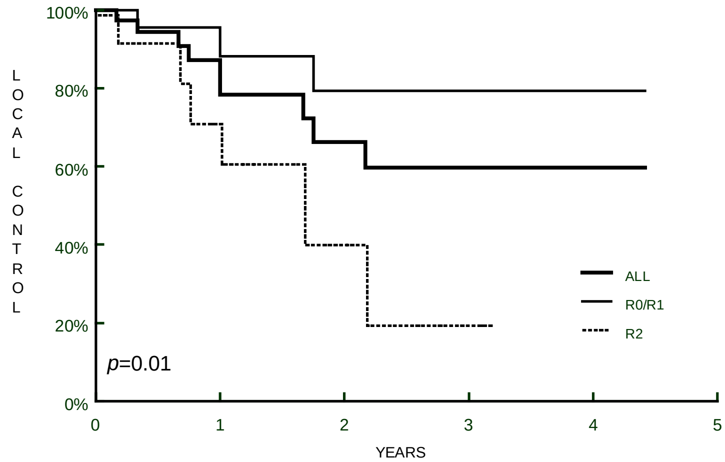

Figure 1. Kaplan-Meier local control curves by radicality of resection (R0/R1 vs. R2).

On final pathology examination, 15 resections (40%) were microscopically radical (R0), of which 12 had received EBRT (including two re-EBRT), and IOERT was administered at a dose of 10 Gy (n = 12) and 15 Gy (n = 3). Eight resections (22%) were microscopically irradical (R1), of which six had received EBRT (including three re-EBRT), and IOERT was administered at a dose of 10 Gy (n = 2), 15 Gy (n = 5) and 17.5 Gy (n = 1). Fourteen patients had R2-resections (35%), of which four had received EBRT, and IOERT was administered at a dose of 15 Gy (n = 6), and 17.5 Gy (n = 8). Preoperative radiation therapy resulted in significantly more radical resections (R0/R1 vs. R2 $p = 0.009$).

Table 3. **Diagnostic and treatment characteristics** (continued)

	No.	(%)
IOERT beam target		
Presacral	9	(24)
Presacro-lateral	3	(8)
Lateral	15	(40)
Ventro-lateral	4	(11)
Ventral	5	(14)
Anaesthesia time (min)		
Mean	490	
Range	240-560	
Intraoperative blood loss (liters)		
Mean	4.1	
Range	0.5-12	
Postoperative hospital stay (days)		
Mean	22	
Range	10-101	

Five of the 37 patients received two IOERT applications: i.e., two separate fields (n = 4) and a boost within the IOERT field (n = 1). The frozen sections had a sensitivity of 91%, a specificity of 100%, and an accuracy of 94%.

Patterns of failure/ survival (Tables 4 and 5)

After a mean follow-up of 31 months (range 2 - 52), 17 patients (46%) are alive with no evidence of disease (NED) and an additional 8 patients (22%) are alive with disease (AWD). Nine patients (24%) died of disease (DD) and 3 patients (8%) died of other causes (DOC).

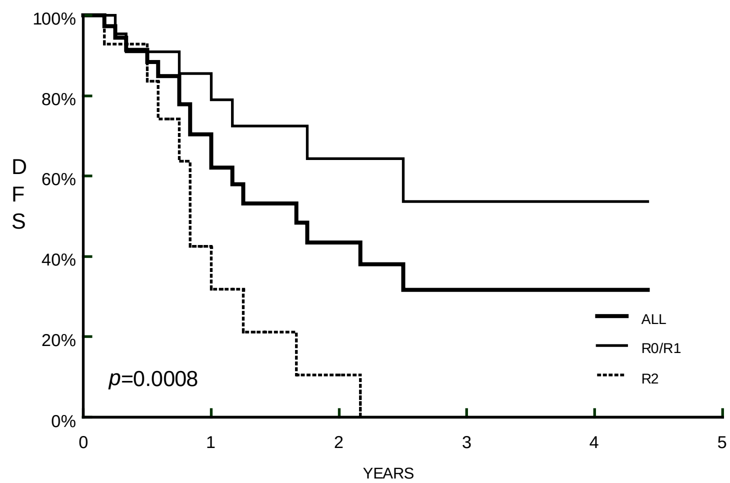

Figure 2. Kaplan-Meier DFS curves by radicality of resection (R0/R1 vs. R2).

Local failures have been documented in 9 patients (24%): seven IOERT infield recurrences and two within the external beam field. Six of these were R2-resections, one a R1 and two a R0-resection. The overall 3-year LC rate was 60% (R0/R1 79% vs. R2 21%) (Fig. 1). Prognostic significant factors on LC were: radicality of resection (R0/R1 vs. R2 $p = 0.01$) and symptoms of pain ($p < 0.05$). Preoperative irradiation vs. none almost reached significance in LC ($p = 0.08$).

Table 4. **Current state and relapses**

	No.	(%)
NED	17	(46)
AWD	8	(22)
DOC	3	(8)
DD	9	(24)
Local recurrences	9	(24)
Metastases	14	(38)

NED = no evidence of disease; AWD = alive with disease;

DOC = death of other cause; DD = death of disease.

Metastases have been observed in 14 patients (40%) at different and sometimes more than one location: peritoneal (n = 4), liver (n = 5), inguinal (n = 4), bone (n = 3) and lung (n = 4) metastases.

Prognostic significant factors for metastases were: radicality of resection (R0/R1 vs. R2, $p = 0.03$), preoperative irradiation vs. none ($p = 0.00007$) and symptoms of pain ($p = 0.02$).

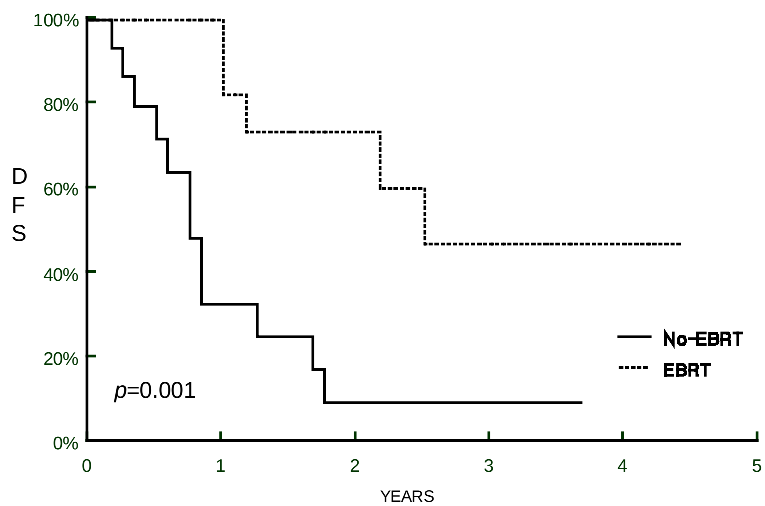

Figure 3. Kaplan-Meier DFS curves by preoperative EBRT vs. no-preoperative EBRT.

The overall 3-year DFS after R0/R1-resection was 54% versus 11% after R2-resection (p = 0.0008); DFS on the whole group was 32% (Fig. 2). Apart from radicality of the resection, DFS was also dependent on preoperative irradiation (p = 0.001) (Fig. 3), symptoms of pain (p = 0.005), and peripheral symptoms (p = 0.03).
The overall 3-year survival rate was 58% (R0/R1 74% vs. R2 35%, $p < 0.05$) (Fig. 4). Other significant factors were preoperative irradiation (p = 0.005), symptoms of pain (p = 0.02), and peripheral symptoms (p = 0.01). Those who died of other causes (DOC) influenced survival. However, cancer-related mortality (DD) also reached significance in: radicality of resection (R0/R1 vs. R2; p<0.05), preoperative irradiation (p=0.005), symptoms of pain (p=0.02) and peripheral symptoms (p=0.03).

Patients with pain or with symptoms of peripheral local recurrences had significantly more macroscopically irradical resections, p = 0.0001 and p = 0.0005 respectively. Prior abdominoperineal resection significantly worsened cancer-related mortality (p = 0.02) compared to prior low anterior and rectosigmoid resections in patients with first recurrences, caused by both a higher local recurrence rate (relative risk 2.1) and a higher metastasis rate (relative risk 2.3).

Table 5. **Statistical results (*P* Value)**

	R0/R1 vs. R2	Preop. EBRT	Pain	Central/peripheral	Prior APR*
Survival	0.05	0.005	0.02	0.01	NS
Cancer mortality	<0.05	0.005	0.02	0.03	0.02
Local control	0.01	0.08	<0.05	NS	NS
Metastasis rate	0.03	0.00007	0.02	NS	NS
DFS	0.0008	0.001	0.005	0.03	NS
R0/R1 vs. R2	-	0.009	0.0001	0.0005	NS

NS = not significant; APR = abdominoperineal resection; * = in primary local recurrences.

Complications (Table 6)

During the operation 5 of 37 patients had a venous plexus bleeding. Postoperatively, one patient died of the sequelae of this bleeding. Two needed packing with gauzes, which could be removed on the second and third postoperative day. In one patient the ureter was severed and once a bladder tear had to be repaired. The mean anesthesia time was 490 minutes (range 240-560), with an average blood loss of 4.1 liter (range 0.5-12) and an average packed cell (500 cc/pc) transfusion of 6.5 (range 0-12).

Postoperative complications were observed in 21 (57%) patients. Most complications could be treated conservatively: urinary retention (n = 7, 19%), wound infections (n = 7), pneumonias (n = 2), a lung embolus (n = 1), and a sepsis of unknown origin treated with antibiotics (n = 1). Reinterventions for postoperative complications were needed in 5 patients (13%); one patient, earlier mentioned, died postoperatively after three reoperations for uncontrollable bleeding of the sacral plexus which resulted in an acute respiratory distress syndrome (ARDS), one patient needed drainage of a wound abscess, one was treated for a small bowel fistula, one for a vesicorectal fistula, and one for a ureterovaginal fistula. The mean hospital stay was 22 days (range 10-101).

Two patients developed, due to the surgery and the radiation, necrosis of the major vessels after, respectively, 2 and 4 months postoperatively. Both died, one immediately after a major bleeding and the other patient as a result of multiple organ failure after several reinterventions for bleeding. Both had a R2-resection and received 17.5 Gy IOERT. In both patients tumor infiltrated in the iliac vessels, which were boosted. Postmortem pathology revealed necrosis, but no tumor residue in the afflicted arteries.

Six patients (16%) developed neuropathy, of which four were classified as grade I (after 15 Gy, n = 2; and 17.5 Gy, n = 2), one as grade II (after 15 Gy), and one as grade III neuropathy (after 17.5 Gy).[35] Other late postoperative complications were: postirradiation stenosis of the ileum (n = 1), radiation enteritis (n = 1), radiation cystitis (n = 1), ureter stenosis which had to be stented (n = 1), a rectovaginal fistula (n = 1), a cutaneous fistula of a Bricker bladder (n = 1), and a vesicovaginal fistula (n = 1).

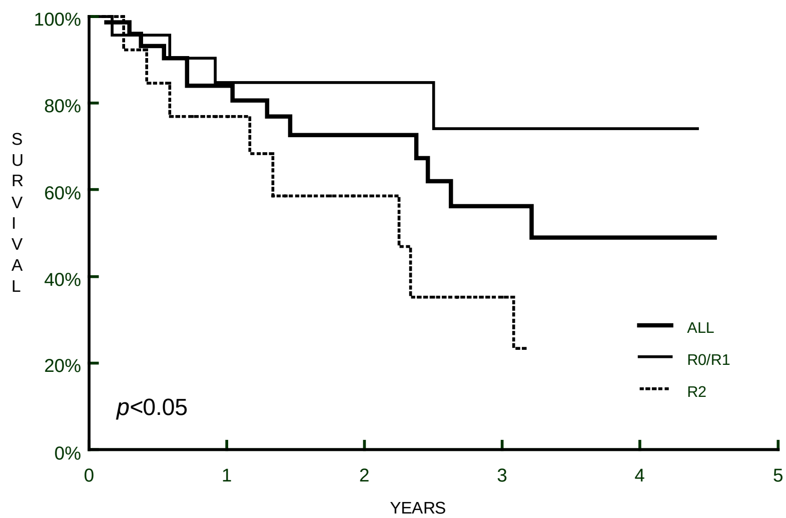

Figure 4. Kaplan-Meier survival curves by radicality of resection (R0/R1 vs. R2).

Table 6. **Complications**

	No.	(%)
Peroperative		
Plexus bleeding	5	(14)
Ureteral injury	1	(3)
Bladder injury	1	(3)
Postoperative		
Hospital death (bleeding)	1	(3)
Wound infections	8	(22)
Urinary retention	7	(19)
Pneumonias	2	(5)
Lung embolus	1	(3)
Sepsis	1	(3)
Small bowel fistula	1	(3)
Vesicorectal fistula	1	(3)
Ureterovaginal fistula	1	(3)
Late postoperative		
Death from bleeding	2	(5)
Lower extremity neuropathy	6	(16)
Irradiation stenosis ileum	1	(3)
Radiation enteritis	1	(3)
Radiation cystitis	1	(3)
Ureter stenosis	1	(3)
Rectovaginal fistula	1	(3)
Vesicovaginal fistula	1	(3)
Bricker bladder fistula	1	(3)
Current function survivors		
Total survivors	25	(68)
Daily function		
Undisturbed	20	(80)
Disturbed	5	(20)
Work		
Restarted	6	(75)
Abandoned	2	(25)
Urinary incontinence	7	(28)

Daily function to some degree was disturbed in 5 (20%) of the current 25 living patients, because of tiredness (n = 3), incontinence (n = 1), and disturbed walking pattern (n = 1). Of the eight patients who worked preoperatively, five restarted their job, one took a lighter job, and two had to abandon their job. Postoperative urinary retention, which was observed in six patients, resolved in three, led to difficulty in starting to urinate in one, and resulted in some stress incontinence in two patients. Four other patients, all operated within the last year, still have continence problems. Two other patients had preoperative incontinence, which deteriorated slightly in one patient.

Discussion

A locally recurrent rectal cancer demands a “non-standard” approach, because a local recurrence is not confined to one anatomical compartment owing to distortion of the anatomical fascial borders after prior surgery. The majority of the patients who present with local recurrence are treated with palliative intent.

The extent and location of the recurrence, the type of the primary surgical resection, and whether or not previous adjuvant radiation therapy has been delivered determine selection of therapy.[20] The high incidence of local recurrences observed in patients with pelvic recurrences undergoing re-resection is partly explained by the high number of incomplete procedures performed due to presacral and/or pelvic sidewall involvement. Nearly 50% of patients who die of their disease do so with tumor confined to the pelvis.[36] This information combined with the relatively less effective systemic therapy for rectal malignancies helps to justify the aggressive combined approaches with surgery and irradiation.

Another problem in locally recurrent rectal cancer is the diagnosis and the staging of the relapse. Physical examination often fails to reveal local recurrences, as the bulk of the tumor is located outside the lumen of the bowel. After an abdominoperineal resection, the situation is even more complex. Moreover, histologically proven local recurrences can not always be obtained.

Imaging of a local recurrence can be difficult due to the distortion of the anatomy and the possible postoperative fibrosis caused by the prior surgery and radiotherapy. MRI has, due to its various pulse sequence techniques, a better soft tissue resolution than CT.[37] However, the demonstration of a local recurrence in a patient with pelvic symptoms can still be difficult, and in some cases in 3-month intervals repeated MRI scans are needed to demonstrate the evidence of a relapse. Furthermore, MRI is essential for the preoperative mapping of the level and the involved quadrants, needed for the planning of the preoperative irradiation and subsequent type of resection. Moreover, a classification of local recurrences, like TNM classification in primary cancers,[38] is not available because of distorted fascias and previously resected lymph nodes, and the fact that alternative lymph routes are unpredictable for the individual patient.

Several studies have shown that the ability to perform a radical resection for recurrent rectal cancer is the most important and only consistent factor to have an impact on survival and local control.[16,21,35,39-41] Preoperative EBRT reduces tumor size and viability, increasing the chances of realizing a radical resection (R0). Because of dose-limiting structures, external irradiation dosages are commonly limited to 45-55 Gy (1.8 to 2 Gy fractions).

Patients with recurrent rectal cancer, who previously received radiation therapy, pose a more difficult problem regarding the radiation tolerance tissue levels. However, significant radiation recovery may occur with time, even in sensitive nongenerating tissue such as the spinal cord.[42] Radiation-induced normal tissue late toxicity, which is the critical limiting factor, can be substantially minimized with application of hyperfractionated irradiation.[43] Therefore the preoperative reirradiation dose is limited, but still can go up to 30 Gy.[2] The radiotherapeutic biologic effectiveness of a single-dose IOERT is equivalent to two or three times the dose of fractionated external beam treatment.[44] Another advantage of IOERT is that dose-limiting structures may be temporarily displaced or shielded with lead.

The intention to treat was to obtain a R0-resection or at least a R1-resection. By combining R0/R1-resection with IOERT, a local radical treatment could be given in 23 of 37 (62%) resected patients. In our successfully treated patients (R0/R1) the 3-year local control, DFS, and survival were 79%, 54%, and 74% respectively. These findings were in contrast with the 3-year local control, DFS, and survival in the R2-resection group, which were 21%, 11%, and 35% respectively. The overall R0/R1/R2 combined results, with a 3-year local control rate of 60%, a 3-year DFS of 32% and a 3-year survival of 58% are comparable to other studies, which use a comparable treatment modality with or without chemotherapy and have a 3-year local control rate ranging from 30% to 75%,[15,21,41,45] a 3-year DFS of 19-33%,[15,21,40,46] and a 3-year survival of 31-56%.[15,20,21,41,45,46]

The most important significant predictor of a favorable outcome was radicality of resection. R0/R1 had a better infield disease control than those with gross residual. Preoperative (re)-EBRT resulted significantly in more radical resections and subsequently in a significantly better outcome with regard to all oncological parameters.

The excluded four patients who had a metastasectomy perioperatively had an unfavorable outcome. Two of them died of metastases at 41 and 43 months. One has a short follow-up. However, denial of this combined treatment plus resection of a solitary metastasis is not justified, since one of them is NED at 43 months, and none of the others had a local recurrence and therefore were successfully palliatively treated.

Complications

Radical ECME can lead to large bleeding, predominantly from the sacral plexus. Rapid intraoperative blood transfusions to compensate blood loss prevent anemia, hypotension, and subsequently ARDS or MOF. In extensive bleeding

intrapelvic gauze packaging for 2 days and nursing in prone position in order to reduce the pressure on the venous plexus, can stop this bleeding.
Ureteral damage occurs in 1% to 10% during the dissection, especially in recurrent cancer because of distorted anatomy and fibrosis, caused by prior surgery, irradiation, or infection.[47] If fibrosis obstructs proper dissection, placement of ureter catheters and the use of cavitron ultrsonic surgical aspiration (CUSA) dissection can reduce accidental ureter severance.

Wound-related morbidity, which occurred in a total of eight patients (22%), is also a most frequent complication in other studies.[15,16,48] An omentoplasty to fill the pelvic space reduces fluid collections and reduces morbidity. Normally, most wound complications resolve in time and therefore are considered a minor problem especially in the long run. Postoperative bladder dysfunction, resulting in urinary retention, which can be caused by surgical and/or radiation-related damage, is usually self-limiting and becomes less prominent in time.

Two patients died of vascular complications, 2 and 4 months postoperatively. The tumor infiltration with disturbance of the architecture of the vessel wall and subsequent necrosis of this tumor after 17.5 Gy IOERT may well have been the reason for these major bleedings. This etiology seems substantiated by the fact that in experimental animal studies normal vessels do not even develop necrosis after IOERT doses of 40 Gy.[49] In the large Mayo IOERT series no vascular deaths were reported although 58 patients received a dose of 17.5 or 20 Gy following R2-resection.[15]

The ureter is a dose-limiting structure with a chance of narrowing and obstructing.[49-52] Therefore we try to keep the ureter out of the IOERT beam. However, when the ureter is located in the area at risk, it is not placed outside the IOERT field. Stents are placed to prevent fibrotic obstruction.

The later sequelae of fistulas are the result of devascularization and radiation necrosis. Peripheral nerves are the main dose-limiting structure for IOERT.[15,49,50,53-55] Symptomatic or objective neuropathy occurred in 6 (16%) patients who all received higher IOERT dosages, ranging from 15 to 17.5 Gy. This is in concordance with the literature in which a higher IOERT dose is related with a higher risk of neuropathy.[15] The observed neuropathy rate in this study is lower than the 32% to 52%,[15,20,56] and higher than the 3% to 10% reported by others.[40,57] However, most studies do not classify the degree of neuropathy, use different definitions, or do not pay much attention to the morbidity, like neuropathy, caused by the multimodality treatment. Because light degrees of neuropathy can be unnoticed and different definitions are confusing, reporting of neuropathy grades is essential.[35]

Functional results were quite good with only 5 of 25 survivors having some degree of disturbance in daily functioning and few persons having incontinence, of which most were operated recently and improvement can be expected in the future.

Prognostic factors

After abdominoperineal resections, the virtual central volume is obliterated and most recurrences easily involve the sidewalls and may be considered peripheral recurrences. Recurrences in the perineal scar, the prostate, or the vaginal septum can correspond with both central and peripheral recurrences. In central recurrent cases significantly more R0/R1 resections were performed (p = 0.0005) and a significantly better survival, cancer-related mortality, and DFS were observed. In concordance with the results reported by Suzuki *et al*. classification of symptoms into asymptomatic, symptomatic, and symptomatic with pain proved to be a significant predictor for survival.[21] Symptoms of pain were also a significant factor for cancer-related mortality, DFS, metastasis rate, and LC. Generally, patients with neuropathy due to tumor ingrowth into the sacral nerve plexus, have a significantly worse LC rate. However, *a priori* selection on symptoms does not seem to be applicable as a conclusive selection criterion, because in these categories also some patients with a favorable outcome have been observed.

Conclusion

Although this study is retrospective, the obtained results seem to indicate that aggressive multimodality treatment improves LC and probably survival at the cost of a high short-term morbidity but an acceptable long-term morbidity. The reported morbidity is comparable to the high incidence of complications after extended pelvic resection alone or in combination with preoperative irradiation for initially unresectable lesions.[16,26,36] In the light of the expected cure rate and the low long-term morbidity, the aggressive combined treatment seems to be justified. This is even truer, when tumor-related morbidity and high mortality are taken into account.

This study confirms that radicality of the surgical procedure is essential to obtain improved locoregional control in patients planned to receive any type of intraoperative irradiation. Preoperative EBRT has been proven to be an essential and significant prerequisite for a successful treatment. Our intention to treat patients curatively, even after a R1-resection, seems to have succeeded, since these results are in line with the results after R0-resections.
Despite the improvement of LC within irradiation fields, local tumor persistence or progression is still common in certain patients. Patients with R2-resections have a worse prognosis than R0/R1-resections.

Appropriate selection of patients for multimodality treatment is crucial to avoid undue morbidity. The following favorable factors were identified to be significantly associated with improved survival: no EBRT in the past, preoperative radiation therapy, low anterior or rectosigmoid resection in the past, no symptoms of pain, and no tumor residue. Efforts have to be directed toward mechanisms that improve tumor exposure, safety of the total dose of irradiation, and resectablity rate. Such mechanisms include modifications on tumor imaging and addition of radiation modifiers (chemoradiation). Efforts have to be directed to reduce the high distant metastases rate. Therefore, development of new schemes of concomitant radiochemotherapy and maintenance chemotherapy might be helpful in solving this problem.

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Chapter 5

Abdominosacral resection for primary irresectable and locally recurrent rectal cancer.

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Guido H.H. Mannaerts, M.D.*, Harm J.T. Rutten, M.D., Ph.D., F.R.C.S.*,
Hendrik Martijn, M.D., Ph.D.‡, Gerbrand J. Groen, M.D., Ph.D.●,
Patrick E.J. Hanssens, M.D.♦, and Theo Wiggers, M.D., Ph.D., F.R.C.S. §

Catharina Hospital, Departments of Surgery * and Radiotherapy ‡,
Eindhoven, The Netherlands.

University Medical Center, Pain Management Center ●, Utrecht,
The Netherlands.

University Hospital Rotterdam/ Daniel den Hoed Cancer Center,
Departments of Radiotherapy ♦ and Surgical Oncology §, Rotterdam,
The Netherlands.

Introduction

Patients with primary rectal cancer extending beyond the fascia propria, or patients with locally recurrent rectal cancer in whom the anatomic tissue planes have been distorted during the primary resection, constitute a difficult surgical problem. If the objective of rectal cancer surgery (to obtain tumor-free radial margins) cannot be met by resection of the complete rectum within its enveloping fascia propria, a primary rectal cancer has to be considered irresectable by the standard total mesorectal excision technique. A radical resection can only be obtained by developing a more extended circumferential margin (extended circumferential margin excision). In locally recurrent cases, especially after abdomino-perineal resection, an extended resection is needed due to the absence of the fascia propria recti.

If the tumor has infiltrated into the sacrum or the lateral pelvic walls, an abdominosacral resection is often necessary. It improves exposure of the dissection and enables en bloc resection of the sacrum and pelvic floor muscles, which in these cases is essential to achieve the necessary complete resection.

This article describes the technical aspects of the abdominosacral resection and its results in a group of patients with locally advanced primary or locally recurrent rectal cancer.

Patients and methods

Between August 1994 and August 1999, 50 patients with locally advanced primary (n=13) or locally recurrent rectal cancer (n=37) underwent composite abdominosacral resection at the Catharina Hospital (n=32) or at the Daniel Den Hoed Cancer Center (n=18). The mean age was 61 (range 33-77) years, and patients were equally divided between both sexes.

Twenty-four patients (65%) with locally recurrent cancer had a previous abdominoperineal resection and 19 patients (51%) in the recurrent group had received pelvic irradiation (median dose, 50.4 Gy; range 25-63 Gy) as part of their primary treatment.

Preoperative external beam radiotherapy (EBRT) was applied in all patients with primary rectal cancer. Eleven patients (85%) received doses of 50.4 Gy (daily fraction (f) of 1.8 Gy; 5 f/ wk), and one received doses of 25 Gy (f = 5 Gy; 5 f / wk). The remaining patient was scheduled for 50.4 Gy but received only 36 Gy because of gastrointestinal complaints.

Twenty-five patients (68%) with recurrent rectal cancer received preoperative EBRT: 50.4 Gy (f = 1.8 Gy; 5 f/wk) when not previously irradiated (n=18) or 30 Gy (f = 2 Gy; 5 f/wk) for reirradiation (n=7). The remaining 12 patients with locally recurrent disease did not receive reirradiation. Technical details of the EBRT technique have been described previously.[1]

Determination of the best surgical approach for a radical resection was predominantly based on CT or MR images. Criteria for an abdominosacral resection in both primary and recurrent cases were invasion extending dorsally into the sacrum or growth into the lateral pelvic walls or pelvic floor muscles and the need for wider dorsal access to improve visualization to enable a complete resection of the tumor. The exclusion criteria for surgery were infiltration into the sciatic notch, S1/S2 involvement, and the presence of irresectable extrapelvic disease.

During surgery, the specimen was examined for possible areas at risk for tumor residue. If there was an area at risk, intraoperative radiotherapy (IORT) was delivered with electron-beam radiotherapy (IOERT) at the Catharina Hospital or with high-dose brachytherapy (IOHDR) at the Daniel den Hoed Cancer Center. Frozen sections, taken to assess the radicality of the resection, determined the IOERT dosage according to the Radiation Therapy Oncology Group protocol:[2] microscopically negative margins, 10 Gy; microscopically positive margins, 15 Gy; and positive margins with gross residual disease (more than 2 square centimeter tumor residue), 17.5 Gy. IOHDR was performed with a flexible intraoperative template and an Iridium-192 source. A dose of 10 Gy was prescribed at 1 cm depth. The target volume was defined as the area at risk with 1-cm margin.[3-5] IOHDR was only performed in cases of microscopically negative but close margins or microscopically positive margins.

Surgical technique

The objective of the technique is the development of free circumferential margins. The circumferential margin consists of three major planes reflecting the different steps in the procedure, i.e., the ventral plane, which is bordered by the bladder and the internal genital organs; the ventrolateral plane with the neurovascular obturator structures, ureters, internal iliac vessels, and branches crossing through the suspensory webs and the intrapelvic part of the obturator internus muscle; and the dorsal and dorsolateral plane, which is in close relation to the levator ani muscles, the intrapelvic attachment of the piriformis muscle, the sacral nerves and vascular plexus, and the sacrum (figures 1,2,3).

A ventral plane has to be developed if the bladder is to be preserved. The female genital organs constitute an easily resectable buffer, whereas in male patients tumor infiltration into the genital organs often means that a ventral plane cannot be developed (figure 1.). In men with dorsolateral extension of the tumor, it is possible to develop the ventral plane guided by Denonvilliers' fascia. Involvement of the vesiculae does not preclude the development of a ventral plane. In case of ventrolateral involvement of one vesicula, transection of the ureter facilitates development of the lateral circumferential margin. Reimplantation of the ureter, if not involved, can be done after mobilization of the bladder with a psoas hitch construction.[6]
When the prostate is not involved, a perineal approach, through a semicircular incision ventral to the anus, can permit the realization of a (partial) ventral plane, facilitating definitive en bloc resection during the later transsacral phase.

Further development of the ventral plane with partial resection of the prostate capsule can better be performed during the transsacral phase, which offers improved exposure. In cases with gross involvement of the ventral structures, a free ventral plane cannot be developed. These cases have to undergo a total pelvic exenteration.

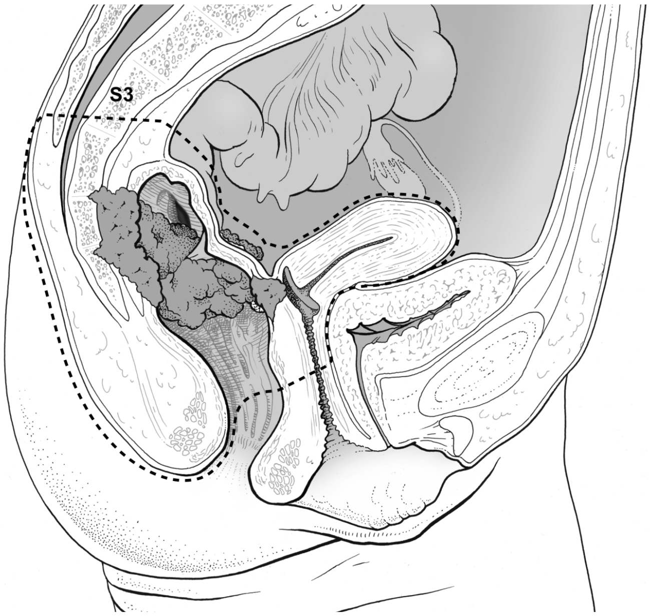

Figure 1. The dotted line indicates the margin of a wide field en bloc resection of tumors with primarily latero-dorsal spread. The dura ends between mid-S1 and mid-S3. If an osteotomy from ventral to dorsal direction was performed at the lower part of S3 during the abdominal phase, the chisel will leave the surface of the sacrum at caudal S3 or proximal S4 level, due to the angle between S3 and S4 in dorsal direction. Therefore, transection at the distal level of S3 does not jeopardize the dura.

The dorsal and dorsolateral dissection is predominantly performed during the transsacral phase. The marking of the level of transection of the sacrum, with a deep cut of the osteotome into the ventral cortical wall, is the only part of the dorsal dissection that is performed during the abdominal phase. Most frequently, the level of transection was just distal of the foramen of S3, because involvement of S2 or a higher level was considered a contraindication for this approach.

A gauze is placed in the presacral space to reduce bleeding from the sacral venous plexus, because this bleeding can better be taken care of during the transsacral phase.

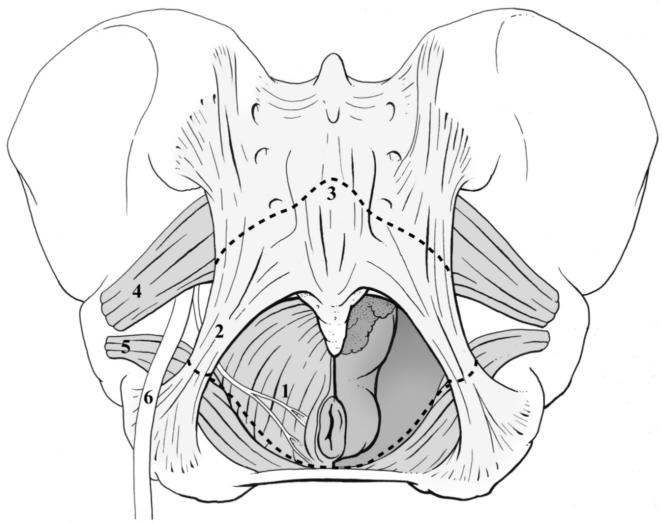

Figure 2. Posterior line of transection. A ventral plane permits introduction of an index finger, which facilitates the identification of the structures that have to be transected: 1. Pelvic floor muscles, 2. Sacrotuberous and the sacrospinous ligaments (last not visible), 3. Third sacral vertebra, 4. Piriformis muscle, 5. Obturator internus muscle, 6. Sciatic nerve, which remains lateral from the dissection line (dotted line).

After the patient is turned from supine to prone position, the procedure continues with the transsacral resection. A dorsal longitudinal midline sacral incision is made from L5 to the perineum and around the anus or anal scar. A full-thickness musculocutaneous flap, including the gluteus maximus and medius muscles, which are perineally dissected from their sacral origins, is raised bilaterally. Then, the sacrotuberous and sacrospinous ligaments are transected near the sacrum in order to gain access to the pelvic floor muscles and the infrapiriformis opening (figure 2.).
Medially to the infrapiriformis opening it is possible to introduce the finger in the presacral space, above the tumor. The level at which the sacral bone was incised by the chisel during the abdominal phase may be palpated. The completion of the sacral osteotomy during the transsacral phase is performed in a V shape to avoid damage to the sacral roots.

The sacrum, the lateral pelvic walls, the retained rectum and the attached viscera are removed en bloc. Especially in cases with a component of lateral spread, a horseshoe-shaped area remains at risk for microscopic residual tumor, bordered by the obturator internus muscle, piriformis muscle with sacral roots and proximal sacrum (figure 3.). This area can be boosted with IOERT or IOHDR.[7]
Closure is straightforward. An omentum flap or muscle flap is placed in the presacral space. If there is no sufficient omentum or in case of a large perineal defect a myocutaneous rectus abdominus flap is rotated in the perineal wound as an alternative.[8,9]

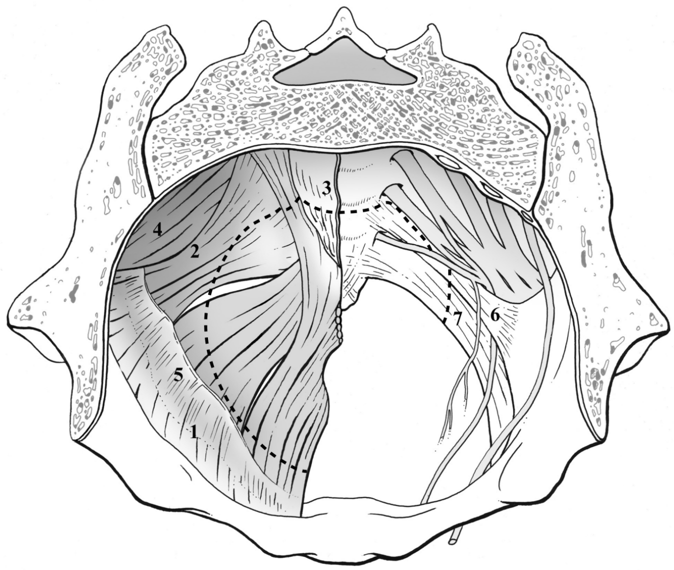

Figure 3. Horseshoe-shaped circumferential margin at risk for tumor residue (dotted line). 1. Arcus tendineus, site of attachment of pelvic floor muscles at the lateral internal obturator fascia, 2. Greater sciatic foramen filled by piriformis muscle and pelvic plexus, 3. Third sacral vertebra, 4. Piriformis muscle, 5. Obturator internus muscle, 6. Sacrospinous ligament, 7. Sacrotuberous ligament.

Results

Operation

The surgical resection margins were microscopically negative in 26 patients (52%), microscopically positive in 18 patients (36%), and positive with gross residual disease in 6 (12%), (primary rectal cancer: 9 negative, 3 microscopically positive, and 1 positive with gross residual disease; recurrent cancer: 17 negative, 15 microscopically positive, and 5 positive with gross residual disease). The sites of these positive margins were as follows: dorsal (n=7), dorsolateral (n=5), lateral (n=5), ventrolateral (n=2), and ventral (n=5) of the rectal tumor. The proximal level of sacral resection was at S3 in 19 patients (38%), S4 in 16 (32%) and S5 in 15 (30%).

Extirpation of other involved organs was performed in 28 patients (56 percent). Resected organs consisted of bladder (n=6), partial bladder (n=1), prostate (n=5), partial prostate (n=4), vagina (n=3), dorsal part vagina (n=11), uterus (n=8), small bowel (n=2), and part of the gluteus muscle (n=1).

A Bricker deviation was constructed in six patients (12%). An omentoplasty was performed in all patients who had sufficient omentum. Two patients had an abdominus muscle flap to fill the perineal defect. Harvesting of the flap is as time-consuming as

an omentoplasty; however, positioning takes approximately an extra 30 minutes.
Abdominosacral resection in patients with primary rectal cancer was combined with IOERT in seven cases (10 Gy, n=4; 15 Gy, n=2; 17.5 Gy, n=1) and with IOHDR (10 Gy) in two cases. Four patients received no IORT.
Twenty patients with recurrent rectal cancer had an abdominosacral resection with IOERT (10 Gy, n=10; 15 Gy, n=6; 17.5 Gy, n=4) and 12 patients had resection with IOHDR (10 Gy). Five patients received no IORT.
Median anaesthesia time, including time for IORT, was 390 minutes (375 minutes in primary and 390 minutes in locally recurrent cancer; range, 210 - 590 minutes). Median blood loss was 3,500 (range 400-10,000) ml and was 3,000 ml in primary resections and 4,200 ml in locally recurrent rectal cancer resections.
Before, during, or just after the abdominosacral operation, seven patients had resection of a solitary liver metastasis (n=4), a lung (n=2), or a local omentum metastasis (n=1). One patient with multiple lung metastases had a palliative resection.

Complications
Intraoperative complications were observed only in the locally recurrent group: three severe plexus bleedings, that needed packing, two ureter lesions, one bladder tear, and one bowel tear.
Postoperatively, the incidence of complications was high (n=41, 82%). Perineal wound sequelae (n=24, 48%) were most notable and required operative drainage in three cases. Almost all perineal wounds healed within several months. Urinary retention/ incontinence (n=9, 18%) was the next most frequent complicaton, which subsided or improved in most patients, although an atonic bladder persisted in two patients. Four patients (8%) developed a peritonitis due to a small bowel lesion and needed a relaparotomy. Pneumonia occurred in two patients, and two patients experienced pyelonephritis. One patient needed drainage of a subphrenic abscess. Three patients developed a fistula: one urethra-perineal, one vesico-vaginal, and one Bricker deviation-perineal fistula. The urethra-perineal fistula in the first patient healed spontaneously. In the two remaining patients, the fistula persisted. One patient developed temporary perineal edema.
There were no hospital deaths. Median hospital stay was 19 (range, 9-129) days.
Treatment-related mortality consisted of two deaths after three and four months, respectively, due to chronic necrosis and infection of the perineal wound.
Late postoperative morbidity consisted of one patient who had the sciatic nerve within the IOERT beam (17.5 Gy) and who developed a grade II neuropathy.[10] Four patients showed grade I neuropathy of the leg. Another patient developed a radiation cystitis after receiving 17.5 Gy IOERT at the prostate. A third patient had a ureter stenosis after having received 50.4 Gy EBRT, surgery, and 10 Gy IOERT (ureter not in beam).

Survival and local control
No significant difference in oncologic outcome between institutions, using either

IOERT or IOHDR, could be established.
After a mean follow-up of 16 (range 2-55) months, Kaplan-Meier recurrence curves show an overall 3-year survival rate of 41%, disease-free survival (DFS) of 31%, and local control rate of 61%.
Completeness of resection (negative vs. positive margins) was a significant factor influencing survival (p=0.04), DFS (p=0.0006), and local control (p=0.0002). Resection with negative circumferential margins and combined treatment (re-EBRT/EBRT and IORT, n=15) resulted in a 3-year survival rate of 94% (p=0.03), DFS of 63% (p=0.003) and local control of 92% (p=0.04).
Patients with positive margins had a 3-year survival rate of 22%, DFS of 0%, and local control of 25%. For patients with microscopically positive margins and
(re-)EBRT plus IORT, these percentages were, respectively, 62%, 41%, and 51%. Seventeen of the 18 patients with microscopically positive margins received IORT. Three of them developed local failure only, five developed distant failure only, and another five developed both local and distant failure.
Preoperative (re-)EBRT for local recurrences resulted in significantly better DFS (p=0.049) than no EBRT.
Previous abdominoperineal resection resulted in significantly more positive resection margins (p=0.02) compared to other prior resections but without significant influence on the outcome.

Three of the 7 patients with synchronous distant metastasis died of disease after 10, 13, and 17 months, respectively. All three developed new distant metastases, and two of them also developed a new local recurrence 8 and 11 months after surgery, respectively. Two other patients were alive with distant disease but without signs of a local recurrence at 20 and 23 months, respectively.
The two remaining patients were alive without tumor relapse at 7 and 18 months after the abdominosacral resection, respectively.

Discussion

Surgery in patients with primary locally advanced rectal cancer, i.e., with tumor beyond the fascia propria, and in patients with locally recurrent rectal cancer in whom the fascia propria is distorted or absent often leads to incomplete resections. Therefore, palliative treatments, most frequently with irradiation, have been considered the first choice for these patients. However, after palliative treatments, most patients will live long enough to develop progression of local disease and subsequently will die with local uncontrollable disease and often without manifest symptomatic metastatic disease.[11-17] Considering this, it seems justified to explore aggressive multimodality treatments: i.e., preoperative EBRT for possible tumor downstaging, extended resection providing a wider access and a wider excision of involved areas, and IORT to boost areas with residual disease.

The abdominosacral resection represents such an extended resection technique and is indicated for possible curative resection in patients with tumor fixation to the sacrum or growth into the dorsolateral pelvic walls. It can also enhance visualization of the dissection in some bulky advanced cases. It allows excellent visualization of important pelvic structures and sacral nerve roots, improves control of venous plexus bleeding, facilitates IORT delivery, and provides an opportunity to obtain a wide en bloc resection of the tumor. Another reason to introduce this technique is that local recurrences, especially after total mesorectal excision, are often situated at a lower level than after conventional techniques. If there is an anastomosis at level of the pelvic floor, distinction between fibrosis to S4 or S5 and tumor can be difficult. Local recurrences after total mesorectal excision are more easily fixed to surrounding structures because of previous excision of the whole mesorectum.

Although several authors reported good results of the abdominosacral resection,[18-32] the use of this technique has not often been reported for irresectable primary and locally recurrent rectal cancers. This might be explained by the technical consideration of this extensive resection and the fact that it is generally considered to cause hazardous complications, i.e., massive operative blood losses; neurologic, urogenital dysfunction; and large musculoskeletal wound defects that frequently result in postoperative wound dehiscence or infection.[20,28]

In this series, a modified abdominosacral resection according to Wanebo et. al.[21,22,33,34] is reported that results in easy access, enabling a wide radical excision in selected patients at the cost of an acceptable morbidity.

Technical nuances of this abdominosacral resection are the performance of the complete operation in one session, in which the patient is turned from supine (abdominal phase) to prone jackknife (transsacral phase) position; determination of the level of sacral transection in the abdominal phase; realization of the distal ventral plane during the abdominal phase through a perineal approach, thus facilitating lateral dissection in the transsacral phase; and control of the sacral venous plexus during the transsacral phase.

The median blood loss was 3.0 liters in primary and 4.2 liters in recurrent rectal cancer resection, which is comparable to the 1.4 to 6.5 liters of blood loss reported in other studies.[19,20,25,28,33,35] Ligation of bilateral internal iliac vessels does not reduce bleeding of the presacral venous plexus.[36] Hemostasis can be achieved most effectively by appropriate hemostatic measures directed to the injured presacral veins and is most convenient via transsacral access after removal of the specimen. If the internal iliac artery is ligated, effort should be made to ligate this artery distal to the first branch (superior gluteal branch) to provide better vascularization of the skin and muscle flaps used for closure of the dorsal wound.

Determination of the sacral osteotomy level during the abdominal phase has the advantage of an easier and more accurate determination of the transection level during the transsacral phase, as well as offering better protection of the pelvic blood vessels. The level of sacral resection should be at S3 or lower, because bilateral transection at a higher level results in destruction of the sacral nerve plexus (root S2 or S3), compromising urogenital function,[22,27,34,37-39] and dorsal flexion of the foot (root S1),[28,32] as well as harming the dural sac (ending between vertebra mid-S1 to mid-S3).[40] In our patient population, the sacrum was frequently (n=19, 38%) cut at S3 providing maximal exposure, without causing any serious neurologic deficit. Bilateral damage of S2 or S3 nerve roots, contributing to the parasympathetic nervi errigentes, will produce major urinary dysfunction with increased urine residue and decreased detrusor function.[22,32,37] However, most patients experience a reasonable revival of function within two months.[27,32,33]

A rectus abdominus muscle flap was used in two patients as an alternative to omentum to fill the sacral cavity, and this added little to the total operative time.[8,9] Other alternatives are the gracilis muscle flap, bilateral tensor fascia lata flaps and gluteus maximus flaps, tensor fascia lata, local peritoneal flap, advancement flaps, rotational skin flaps, and Vicryl mesh when there is no autologous tissue to cover the pelvic floor.[22,28,30,33,41-45] A non-resorbable knitted polypropylene mesh is a less desirable option because of frequent wound infections in this area.[39]

The ureter is particularly at risk during the transsacral phase. This risk is increased in patients with locally recurrent rectal cancer because of disturbance of the anatomic pathways and increased fibrosis caused by previous irradiation and surgery. If a ureter lesion is recognized during the operation, a double J luminal catheter can be inserted to prevent postoperative leakage. Pre- or intraoperative prophylactic placement of a double J ureter catheter facilitates the dissection. An alternative to prevent necrosis of the ureter owning to devascularization is a more proximal transection and reimplantation of the ureter.

No hospital death was observed; however, two patients (4%) died of perineal wound sequelae, three and four months after surgery, respectively. This is comparable to reported perioperative mortality rates of less than 9%.[14,19,20,30,31,34,46,47] The incidence of postoperative complications was higher than previously published morbidity rates of between 25% and 69%.[14,28,31,42,46] Wound-related morbidity, which occurred in 48% of the patients, was also the most frequent complication in other studies with a range of 38% to 51%,[31,34,46] although this resolves in most patients over time. Voiding problems are not frequently reported in studies on abdominosacral resection. However, damage, especially to the urinary nerves, is very likely. Postoperative voiding problems were observed in 18% of patients in the present study.

Clinical studies have ascertained that morbidity and mortality of surgery are not increased markedly by the addition of IORT.[47-49] The peripheral nerve is the main dose-limiting structure for IORT.[50-52] Although IORT doses of 10 to 20 Gy can be administered safely, the risk of neuropathy seems to increase above 12.5 Gy.[17] Symptomatic neuropathy occurred in 10% of patients, which is in line with the 3 to 52% neuropathy rate reported by others.[52-56] Four of our five patients had light neuropathic complaints (grade I). Furthermore, ureteral stenosis or obstruction can be caused by IORT.[52,57-61] Reported ureteral stenosis rates located in the IORT area range from 36% to 44%.[52,53,57,58-61] However, it is often possible to keep the ureters out of the IORT field or to shield them with lead. Prophylactic ureteral stents can be placed, or stents can be placed if subsequent obstruction develops, to protect or overcome ureteral obstruction and preserve renal function. In this present study, ureter stenosis and cystitis were only observed once.

Our intention to treat, to achieve clear or microscopically positive resection margins that could be curatively treated by IORT, was accomplished in 88% of the patients.

Reported salvage rates range from 18% to 30%.[25,28,30,32,34] This series, with a perioperative metastases rate of 14%, shows an overall 3-year survival rate of 41%, a DFS rate of 31%, and a local control rate of 61%. Completeness of resection, which was achieved in 52% of the resections, significantly influenced survival (p=0.04), DFS (p=0.0006), and local control (p=0.0002). Complete resection in combination with EBRT and IORT resulted in a 3-year survival of 94% (p=0.03), DFS of 63% (p=0.0003) and local control rate of 92% (p=0.04).

Abdominosacral resection with IORT in patients with macroscopic residual or irresectable disease is questionable considering the magnitude of the treatment. Furthermore, IORT does not seem to improve outcome in these patients. Therefore, this type of surgery is not undertaken if macroscopic residual disease or irresectability is anticipated. Other palliative treatments must be considered.

Solitary distant metastases do not have an a priori dismal prognosis. After appropriate meticulous staging, some patients may be candidates for resection of the solitary metastasis as well as the local recurrence.

Better imaging techniques may be helpful in selecting the appropriate resection plane. During the operation, it is very hard to distinguish tumor deposits from fibrosis. Radioimmunoguided surgery has been reported to be efficient in discriminating between tumor-residue and fibrosis.[62] Neoadjuvant treatment will be improved by the use of new radiosensitizers, resulting in a higher rate of complete resections.

Conclusion

Many patients with locally advanced primary or locally recurrent rectal cancer will die with disabling disease without ever developing metastatic disease. Palliative irradiation and/ or chemotherapy will only give temporary relief. On the other hand, aggressive multimodality local treatments (preoperative EBRT, extensive surgery and IORT) can render a considerable percentage of these tumors resectable for cure. After proper selection, and especially when there is involvement of the dorsolateral pelvic walls or the sacrum, abdominosacral resections can be an integral part of such treatment. They provide technical access that results in good visualization of the resection margins, and they are well tolerated, with acceptable morbidity and mortality. Centralization of these patients at facilities that have surgical experience and are equipped for IOERT or

IOHDR is mandatory.

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Chapter 6

Anaesthesia for advanced rectal cancer patients treated with combined major resections and intraoperative radiotherapy.

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Guido H.H. Mannaerts, M.D.*, André A.J. van Zundert, M.D., Ph.D.§, Vera C.H. Meeusen, C.R.N.A.§, Hendrik Martijn, M.D., Ph.D.‡, and Harm J.T. Rutten, M.D., Ph.D., F.R.C.S.*

Catharina Hospital, Departments of Surgery *, Anaesthesiology § and Radiotherapy ‡, Eindhoven, The Netherlands.

Introduction

Following resection of a rectal cancer, tumor re-growth within the pelvis (local recurrence) occurs in 10-20% of the patients.[1] This rate increases in locally advanced primary tumor cases, as more often incomplete resection margins are obtained. A local recurrence is difficult to deal with and is often treated palliatively. Many patients outlive their palliative treatment and die of local tumor progression with symptoms of severe pain, bleeding and ulceration of the perineum.[2]

Aggressive multimodality treatment, consisting of high dose pre-operative external beam radiotherapy (EBRT) to reduce tumor size and improve resectability; extended surgery to obtain a radical margin excision; and intraoperative radiation therapy (IORT) as a boost to irradiate possible tumor residue, decreases the high local failure rate and improves survival in patients with locally advanced primary or locally recurrent rectal cancer.[3-7]

This procedure is associated with major and often rapid blood loss, hypothermia, prolonged surgical intervention time, intraoperative change of position of the patient on the operation table and transport of the patient to the IORT-applicator with temporary remote monitoring of the patient during the IORT-boosting.

Limited experience in the specific anaesthetic support of these patients is available, as this technique is being applied in only few major cancer centers.
The aim of this report was to discuss the anaesthetic management and to analyze the perioperative results in patients receiving multimodality treatment for locally advanced primary or locally recurrent rectal cancer.

Methods

Between February 1994 and March 2000, 106 patients without demonstrated distant metastases received a multimodality treatment for rectal cancer. Fifty patients (47%) had a locally advanced primary tumor and fifty-six patients (53%) a local recurrence of rectal cancer after prior surgery. Patient demographics and treatments data are listed in Tables 1 and 2.

The anaesthetic, surgical and radiotherapeutic medical charts of all patient were reviewed retrospectively by an anaesthesiologist evaluating the perioperative results of the treatment (laboratory results, medication, monitoring, resuscitation, duration of anaesthesia, surgery and ICU-stay, complications, and re-interventions).

A combined general-epidural anaesthesia technique was used. Prior to induction, all patients received a lumbar epidural catheter and continuous epidural infusion of bupivacaine 0.125% and sufentanil 1 µg/mL at a rate of 7 mL/ hr. A pulmonary artery wedge pressure and or central venous catheter was introduced through the internal jugular vein at the anaesthesiologist's discretion and the patient's medical history.

Table 1. **Demographic and Pre-operative Data**

	n	Range/%
Total number	106	
Age (mean/ range in years)	63	36-85
Sex M / F	64 / 42	
Length (mean/ range in cm)	172	148-203
Weight (mean/ range in kg)	70	47-103
ASA classification ASA II	76	(72%)
ASA III	30	(28%)
Positive history Cardiac	20	(19%)
Pulmonary	10	(9%)
Creatinine (mean/ range in µg/L)	86	51-193
Hemoglobin (mean/ range in mmol/L)	7.7	5.2-9.8

At induction, patients received 0.3 mg/kg etomidate, fentanyl 0.75 µg/kg, pancuroniumbromide 0.1 mg/kg and 40/60 N2O/O2. After intubation, sevoflurane inhalation or a propofol infusion was started for maintenance of anaesthesia according to the choice made by the attending anaesthesiologist. Pancuronium and fentanyl were administered according to the needs of the patient. Cefuroxim (1500 mg) and metronidazol (500 mg) were given I.V. as standard antibiotic prophylaxis.

Hemodynamic monitoring consisted of invasive arterial blood pressure, heart rate, central venous pressure (CVP), ECG, urine output, oxygen saturation via pulse oximetry, and if available, cardiac index (CI), systemic and pulmonary vascular resistance (SVR/ PVR). In order to prevent heat-loss during the operation, a warmed blanket (Bair Hugger®) on the upper part of the body (thorax, face, arms), a heated mattress, thermo-drapes around the legs and fluid warmers were used. Two large-bored peripheral I.V. lines (14G) were introduced, to administer warmed saline and colloids (Haemacell®), and a SIMS Level 1® was connected to a central venous line to administer fast normothermic fluids or blood.

The following parameters were recorded: arterial blood pressure, CVP, heart rate, pulmonary artery diastolic blood pressure, cardiac index, systemic and pulmonary vascular resistance. Results of the urinary output, peripheral oxygen saturation, nasopharyngeal temperature, blood loss and fluid balance were also registered, as well as the results of blood tests, consisting of hemoglobin, sodium, potassium, blood gasses, glucose, urea and creatinine levels.

Table 2. **Tumor Type and Treatment Assets**

	n	(%)
Type of rectal carcinoma		
Locally advanced primary	50	(47)
Locally recurrent	56	(53)
Treatment characteristics		
Pre-operative EBRT		
No re-irradiation	20	(19)
Re-irradiation (30 Gy)*	10	(9)
Full irradiation (45-50 Gy)	76	(72)
Combined with chemotherapy**	24	(23)
Surgery		
Low anterior resection	21	(20)
Abdominoperineal resection	38	(36)
Exenteration (bladder/ int. genitals)	16	(15)
Abdominosacral resection	31	(29)
IOERT doses		
10 Gy	64	(60)
12.5 Gy	4	(4)
15 Gy	24	(23)
17.5 Gy	14	(13)

* Re-irradiation of previously irradiated patients has been performed since the end of 1997.

** pre-operative radiotherapy has been combined with chemotherapy since the end of 1998.

During surgery, extensive blood loss was counterbalanced by rapid I.V. fluid resuscitation (electrolyte and colloid solutions, packed red cells and if necessary other blood products) in order to improve circulating volume and to maintain coagulation. Fluid administration is based on central venous pressure, systemic blood pressure, hemoglobin results, heart rate, urine output, blood loss, and the status of the surgical intervention.

The position of all patients had to be changed several times during the procedure. Depending on the type of resection, position was changed from supine to jackknife and even prone position (in case of abdominosacral resection). Transport to and from the IORT linear accelerator presented an additional problem in the anaesthetized patients. The patient as well as the attached monitoring devices had to be moved 5 meters within the same room. During the IORT administration (doses ranged from 10 to 17.5 Gy) all personnel had to leave the treatment room for approximately ten minutes for radiation safety reasons, where they were protected by a 150 cm thick concrete wall. During IORT, radiation is delivered with electrons through a tube mounted on the linear accelerator.

The tube is in direct contact with the area to boost guiding the electron beam to the target area and keeping radiosensitive normal tissue outside the beam. Radiosensitive structures within the scope of the tube may be surgically displaced, or be shielded by lead.

A camera visualizing the patient and all control panels, and an intercom transferring all sounds and alarms were used to monitor the patient from the adjacent room. The irradiation could be stopped at any time if an intervention was considered necessary.

An inhalation agent or a propofol infusion, combined with an extra bolus of pancurorium and fentanyl, allowed using high inspirated concentrations of oxygen during IORT, while preventing awareness or muscle contractions. This is felt to be beneficial since tissue hyperoxia enhances the effectiveness of irradiation.[8] After returning the patient to the original supine position, surgery was completed, the patient was stabilized and prepared for transfer to the ICU.

Table 3. **Peroperative Data**

	Mean	**S.D.**	**Range**
Duration anaesthesia (hours)	6.1	±1.3	3-10½
Duration surgery (hours)	5.2	±1.3	2½-9½
CI (L/min)	2.8	±0.6	1.8-4.0
SVR (dynes. sec. cm^{-5})	1159	±458	524-2275
PVR (dynes. sec. cm^{-5})	87	±68	10-275
Lowest systole (mm Hg)	85	±12	50-120
Highest systole (mm Hg)	136	±18	100-195
Pulm. diastole (mm Hg)	15	±4	6-30
Mean heart rate (/min)	85	±18	50-145
Lowest saturation (%)	97	±1	90-99
Lowest temperature (^{0}C)	35.2	±0.6	33.9-37.2
Total blood loss (L)	3.6	±2.5	0.4-14
Total blood transfusion (U)	7.5	±6.0	0-24
Crystalloids + Colloids (L)	10.4	±3.8	4.5-28
Urinary output (mL/h)	186	±126	23-727
Lowest hemoglob. (mmol/L)	5.3	±0.8	3.5-7.2
Lowest potassium (mmol/L)	3.5	±0.4	2.4-4.4
Lowest sodium (mmol/L)	139	±4	130-150
Lowest arterial pH	7.30	±0.24	7.1-7.5
pCO2 (mm Hg)	39	±5	29-52
pO2 (mm Hg)	168	±73	45-424
HCO3 (mmol/L)	19.2	±2.4	10.8-27

Results

The mean duration of anaesthesia was 6 ±1.3 hours (range 3-10½ hrs) and the mean duration of surgery 5.2 ±1.3 hours (range 2½-9½ hrs). The mean blood loss was 3.6 ±2.5 liters (range 0.4-14 L), which was compensated by a mean crystalloid and colloid infusion of 10.4 ±3.8 liters and a mean blood transfusion of 7.5 ±6.0 units. A pulmonary wedge catheter was used in 27 patients (25%).The CI, SVR, PVR and urine production were kept all within acceptable limits. The mean lowest temperatures measured during operation were 35.2 ±0.6 ^{0}C (range 33.9-37.2 ^{0}C) and 35.6 ±1.0 ^{0}C (range 36.3-38.9 ^{0}C) at the ICU. The peroperative and ICU results are listed in Tables 3 and 4.

Table 4. **Postoperative Data at ICU and Hospital Stay**

	Mean	**S.D.**	**Range**
Intensive care stay (hours)	45	±119	0-840
Intubation time (hours)	17	±54	0-480
CI (L/min)	3.0	±0.8	2.9-5.2
SVR (dynes. sec. cm^{-5})	1174	±435	120-2300
PVR (dynes. sec. cm^{-5})	99	±43	25-226
Lowest systole (mm Hg)	99	±15	60-140
Highest systole (mm Hg)	150	±24	105-210
Heart rate	98	±21	30-160
Lowest temperature (^{0}C)	35.6	±1.0	33.1-37.4
Highest temperature (^{0}C)	37.6	±0.6	36.3-38.9
Total blood loss (L)	1.2	±2.0	0.7-13
Total blood transfusion (U)	2.5	±5.9	0-32
Crystalloids + Colloids (L)	0.2	±0.8	0.2-0.6
Urinary output (mL/h)	132	±69	66-322
Lowest hemoglob. (mmol/L)	6.2	±0.9	3.7-8.3
Lowest potassium (mmol/L)	3.7	±0.5	2.7-5.3
Lowest sodium (mmol/L)	138	±4	124-149
Creatinine (mm Hg)	81	±36	42-351
Lowest arterial pH	7.30	±0.24	7.15-7.55
pCO2 (mm Hg)	40	±6	18-73
pO2 (mm Hg)	150	±36	85-234
HCO3 (mmol/L)	20.6	±8.4	14.2-96
Hospital stay (days)	20	±10	6-61

During the operation, sacral plexus bleeding was observed in seven patients (7%) and urological damage in five patients (5%). None of the intraoperative radiation procedures had to be interrupted.

Table 5. **Treatment-induced Mortality**

	Location of onset	Cause	Time from operation to death (days)
General exhaustion			
Patient no. 1	Home	Depression/ starvation	51
Patient no. 2	Home	Depression/ starvation	77
Bleeding causing shock			
Patient no. 3	Home	New local recurrence	167
Patient no. 4	Home	Late necrosis	73
Bleeding followed by ARDS/MOF			
Patient no. 5	Hospital	Repeated sacral plexus bleeding	34
Patient no. 6	Home	Repeated bleeding due to necrosis	131
Patient no. 7	Hospital	Bleeding due to anticoagulant overshooting	38
Presacral abscess			
Patient no. 8	Home	Chronic presacral abscess	205
Patient no. 9	Home	Sepsis from a presacral abscess	182

The mean overall ICU-stay was 45 ±119 hours (range 5-840 hrs). The majority of the patients (94%) were hemodynamically and respiratory stable enough to be discharged from the ICU to the ward within three days. Four patients (4%) stayed 3-7 days in the ICU, as a result of repeated perineal bleeding, bowel perforation or ARDS. Only two patients (2%) had to stay longer than one week and died in the end due to direct postoperative complications in the ICU (Table 5). One patient was anticoagulated excessively, which resulted in major blood loss one day postoperatively. Two reexplorations were needed, followed by severe ARDS leading to death 38 days postoperatively. Another patient had repeated bleeding from the sacral plexus and received three reexplorations complicated by pneumonia, pulmonary embolism and finally ARDS and died 34 days postoperatively.

No other hospital deaths occurred. Seventy-two patients (68%) experienced one or more complications. The most serious postoperative complications were four cases of sepsis (due to leakage of a bowel anastomosis in two, cholecystitis in one, and another of unknown origin), requiring temporary dialysis for renal insufficiency in one patient; one case of ARDS following a peroperative plexus bleeding, pulmonary embolism and pneumonia; and three patients needed surgical intervention (ileus, gastric perforation and bowel perforation). All complications are listed in Table 6. A surgical reexploration was performed in 20 patients (Table 7). The mean overall hospital stay was 20 ±10 days (range 6-61 days).

Table 6. **Complications***

	n	(%)
Peroperative complications		
Anaesthetic	0	(0)
Surgical		
Sacral plexus bleeding	7	(7)
Ureter damage	3	(3)
Urethra damage	1	(1)
Bladder damage	1	(1)
Mortality	0	(0)
Postoperative complications		
General		
ARDS	3	(3)
Sepsis	4	(4)
MOF	1	(1)
Pulmonary embolism	2	(2)
Pneumonia	3	(3)
Cardiac decompensation	1	(1)
Insufficient kidney function	1	(1)
Cholecystitis	1	(1)
Gastric perforation	1	(1)
DVT	3	(3)
Decubitus	1	(1)
Urinary tract infection	14	(13)
Surgical		
Wound sequelae	12	(11)
Bleeding	4	(4)
Fascia dehiscence	1	(1)
Leakage of bowel anastomosis	2	(2)
Presacral abscess	3	(3)
Ileus	1	(1)
Fistulae	6	(6)
Voiding dysfunction	23	(22)
Radiotherapeutical		
Sacral plexus neuropathy	12	(11)
Radiation cystitis	1	(1)
Stenotic ileum	1	(1)
Ureter stenosis	1	(1)
Hospital mortality	2	(2)

* Including the complications listed in Table 5.

Seven patients (7%) died after being discharged from the hospital due to late complications (Table 5). One patient was readmitted to the ICU after experiencing perineal bleeding 89 days after the operation. Five surgical interventions were indicated in an attempt to stop the persistent bleeding caused by major pelvic vascular necrosis, after which the patient finally died of MOF, 131 days postoperatively.

Table 7. **Re-interventions**

	n	(%)
Bleeding		
Number of patients involved	4	(4)
Number of re-operations	12	
Drainage of presacral abscess	3	(3)
AP revision	3	(3)
Repair of anastomotic leakage	2	(2)
Removal of gauze packing	2	(2)
Cholecystectomy	1	(1)
Repair of gastric perforation	1	(1)
Adhesiolysis	1	(1)
Correction fistulae	3	(3)

Two other patients suddenly developed a major perineal bleeding at home as a result of necrosis within the pelvis in one (73 days postoperatively) and as a result of a local tumor recurrence in the other patient (163 days postoperatively) causing death. Another two patients died (51 and 77 days postoperatively), due to general exhaustion and starvation, as both patients refused to take any more food. The remaining two patients died, respectively 182 and 205 days postoperatively, as a result of a chronic presacral abscess.

The oncological outcome in terms of survival, disease free survival and local control (control on pelvic tumor recurrence) is listed in Table 8.[3,4]

Table 8. **Overall 3-year Results (Kaplan-Meijer)**

Locally advanced primary rectal cancer	
Survival	72%
Disease free survival	65%
Local tumor control	82%
Locally recurrent rectal cancer	
Survival	58%
Disease free survival	32%
Local tumor control	60%

Discussion

Multimodality treatment including pre-operative irradiation, followed by extensive surgery and intraoperative radiotherapy, has been used with increasing frequency in patients with locally advanced primary and locally recurrent rectal cancer, as it improves local control and survival in these patient groups in comparison with more conservative treatments.[3-7] However, this intraoperative radiotherapy containing multimodality treatment is only used in a few hospitals in the world, as most of the hospitals do not have these IORT facilities. Very little is known about the specific anaesthetic requirements of this treatment.

The anaesthesiologist is faced with several problems. The extensive surgery is associated with a potential of acute extensive blood loss. In this study the mean blood loss was 3.6 liters. Rapid massive administration of crystalloids, colloids and blood products are needed to avoid hemodynamic instability, which can lead to shock, ARDS, MOF, myocardial infarction and renal insufficiency.[9,10] Coagulation and electrolyte disturbances, caused by massive volume shifts, have to be corrected as well. Especially if a sacral venous plexus bleeding occurs severe rapid blood loss can be expected. A central venous line and two large-bored peripheral I.V. lines were used to secure the possibility of rapid transfusion. Urine output was acceptable in most patients, however it could not always be measured as the bladder was removed in eleven patients or the ureter was detached in three patients. In addition to urine output, CVP was used as an indicator for the hydration status. Aggressive resuscitation with warmed fluid and blood products minimized shock.

Massive transfusion and prolonged large body surface exposure, during extensive surgery can also cause hypothermia. Heat-loss was compensated adequately using fluid warmers, including the SIMS level-1®, thermo-drapes, a heated mattress and a warmed blanket (Bair-Hugger®).

The change of position of the patient during the procedure and the transport of the intubated patient, together with the anaesthetic equipment to the linear accelerator for IORT-application and back, is a period of potential instability.[11-14] Stable cardiovascular, respiratory and metabolic conditions, and adequate analgesia was a prerequisite for the transfer of the patient.[14] In this study transportation to the linear accelerator was 5 meters within the same room. Most centers, however, require interdepartmental transfer of the patient in order to utilize IORT.

Remote monitoring of the patient during the approximately 10 min-period of IORT application complicates the procedure even more. The patient as well as the monitors are observed by a close circuit camera transmission in an adjacent room. Access to the patient is possible within seconds if necessary, and is without loss of efficacy of the IORT. Problems with the monitoring equipment or with the patients' medical situation during the IORT application were not encountered.

During IORT administration, the patient is hyperoxygenated (FIO_2 1.0) to improve the effect of the irradiation on tumor cells.[8] Therefore, either an inhalation anaesthetic or a continuous propofol infusion is indicated to prevent awareness. Pancuronium and fentanyl are administered to prevent muscle contractions. The patient should not move during the intraoperative irradiation, otherwise the electron beam may be diverted from the target area.

IORT is to be delivered during the operative procedure, as the resection area at risk for possible residue of cancer can then be assessed more accurately in order to avoid a second operation. IORT can be delivered with a linear electron accelerator as intraoperative electron beam radiotherapy (IOERT), as in this study, or with an Iridium template as a high dose rate brachytherapy (IOHDR), which is considered equally effective but more complicated and time-consuming.[15] In both cases, however, irradiation has to be performed in a room with concrete walls with a thickness of at least 20 cm or a lead-shielded operating room, otherwise the radiation dose would exceed legal limits outside the IORT suite. In this study a special dedicated radiotherapy room with built-in surgery facilities at the radiation department was used. The fact that this dedicated operation room is at a remote area from the main OR-complex has its disadvantages. Pre-operative preparation, i.e., transport of monitors, ventilator, equipment, drugs and surgical instruments to this operation room, takes at least two hours. Blood lab results can not be obtained as quickly, the blood storage refrigerator is not nearby and extra personnel, in case of severe shock, resuscitation or catastrophe is not readily available and takes also more time. Furthermore, postoperative transportation of the patient to the ICU takes more time.

The potential complications of radical operative procedures for rectal carcinoma cover the entire spectrum of complications encountered during major abdominal operations. Perioperative mortality rate (30-days) ranges from 0 to 18% and operative morbidity rate ranges from 10 to 69 percent depending of the extent of the resection.[16-24]

In this study no peri-operative death was observed within the first 24 hours. Two late in-hospital deaths occurred as a result of uncontrolled hemorrhage. Others have reported severe postoperative hemorrhage leading to death following extensive pelvic resections.[18,25-27] In this study, this might have been prevented in one patient, who had an overshoot of anticoagulantia during the immediate postoperative period. If control of hemorrhage can not be achieved peroperatively, packing of the pelvis and nursing the patient in the prone position in the ICU, to reduce the pressure on the pelvic venous plexus, can be the solution as was performed in two patients. Furthermore, the epidural catheter reduces the venous plexus pressure as a welcome side effect.

The anaesthetic complication rate was low. Ninety-four percent of the patients recovered well in the ICU and were discharged to the ward within 3 days. Seven patients (7%) died after being discharged from the hospital (51-205 days postoperatively), in most cases as a result of necrosis within the small pelvis.

In conclusion, adequate preparation and (remote-) monitoring, early aggressive transfusion and proper multidisciplinary communication can avoid peri-operative complications.

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Chapter 7

Urological and sexual morbidity following aggressive multimodality treatment for locally advanced primary and locally recurrent rectal cancer.

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Guido H.H. Mannaerts, M.D.*, Marlies P. Schijven, M.D., M.Sc.*,
Ad Hendrikx, M.D., Ph.D.□, Hendrik Martijn, M.D., Ph.D.‡,
Harm J.T. Rutten, M.D., Ph.D., F.R.C.S.*, and Theo Wiggers, M.D., Ph.D., F.R.C.S.§

Catharina Hospital, Departments of Surgery *, Urology ♦ and Radiotherapy ‡, Eindhoven, The Netherlands.

University Hospital Rotterdam/ Daniel den Hoed Cancer Center,
Department of Surgical Oncology §, Rotterdam, The Netherlands.

Introduction

Conventional low anterior and abdomino-perineal resection for rectal cancer is associated significantly with local recurrence, sexual and voiding dysfunction.[1-3] The autonomous nerve-preserving total mesorectal excision (TME) technique has proven to reduce local recurrence rates from up to 35% to less than 10%, whilst preserving urogential function.[2-8]

However, in locally advanced primary rectal carcinomas, TME may be insufficient to obtain a curative resection. As in locally recurrent rectal cancer, the tumor is not confined to the rectal compartment, due to severance of the anatomical fascial planes. Hence, extended circumferential margins are required to achieve a complete resection in both presentations of rectal cancer. Multimodality treatment, combining preoperative external beam radiation therapy (EBRT), in order to reduce the tumor size, with extended surgery, aiming for a complete tumor resection, followed by intraoperative radiotherapy (IORT), to boost the resection area at risk for tumor residue, results in curation in 46-62% of patients with locally advanced primary and in 19-21% of patients with locally recurrent rectal cancer.[3,9-15]
Multimodality treatment has its price. Both radiotherapy and extended surgery can increase the probability of damage to the urogenital nerves and organs, which results in voiding and sexual dysfunction.[1,16,17]

The purpose of this study is to assess the long-term urogenital outcome following multimodality treatment.

Patients & methods

Patients

From February 1994 to August 1999, 121 patients underwent multimodality treatment in the Catharina Hospital and the Daniel den Hoed Cancer Center: 55 patients having locally advanced primary (32 males and 23 females), and 66 patients having locally recurrent rectal cancer (41 males and 25 females). The median overall age was 63 years (range 39-86).

The multimodality treatment consisted of high dose preoperative radiotherapy (50.4 Gy or 30 Gy, if reirradiated), extended circumferential margin excision (ECME) and IORT (10-17.5 Gy).[18,19] The IORT was delivered as intraoperative electron beam radiotherapy (IOERT) in the Catharina Hospital and as intraoperative high dose rate brachy therapy (IOHDR) in the Daniel den Hoed Cancer Center. The specific details of the multimodality treatment are listed in
Table 1.

Table 1. **Patient and treatment characteristics**

	Locally advanced primary		Locally recurrent	
	No.	**(%)**	**No.**	**(%)**
Total number	55	(45)	66	(55)
Age (years)				
Median	64		61	
Range	36-86		39-82	
Sex				
Male	32	(26)	41	(34)
Female	23	(19)	25	(21)
Prior treatment				
Irradiation	-		25	(38)
Mean (Gy)	-		50.4	
Range (Gy)	-		25-66	
Surgical procedure				
Low anterior resection	-		40	(61)
Abdominoperineal resection	-		23	(35)
Exenteration	-		3	(4)
Ileum conduit	-		3	(4)
Multimodality treatment				
Irradiation (n)*	55	(100)	48	(73)
Median (Gy)	50.4		50	
Range (Gy)	25-61		16-50.4	
Surgical procedure				
Low anterior resection	15	(27)	7	(11)
Abdominoperineal resection	20	(36)	21	(32)
Abdominosacral resection	12	(22)	26	(39)
Exenteration	8	(15)	12	(18)
Ileum conduit	4	(7)	9	(12)
Radicality resection				
Negative margins	45	(82)	31	(47)
Microscopical positive margins	6	(10)	19	(29)
Macroscopical positive margins	4	(8)	16	(24)
IORT**				
IOERT (n)	45	(82)	49	(74)
10 Gy	38	(66)	24	(33)
12.5 Gy	1	(2)	-	
15 Gy	6	(10)	17	(23)
17.5 Gy	2	(4)	13	(18)
IOHDR				
10 Gy	10	(18)	17	(26)

* Seven patients in the locally recurrent group received 30 Gy reirradiation.
** Two locally advanced primary and 5 locally recurrent patients received two IORT applications.

Methods

All 121 surgical and urological patient records, receiving multimodality treatment, were reviewed for previous radiotherapy and surgical rectal treatment, current radiotherapy and surgical treatment, and urological operative and postoperative complications caused by multimodality treatment. Scoring of late postoperative complications was stopped if a patient developed a local recurrence.

Analysis of long-term urogenital morbidity was measured by means of a structured questionnaire, sent to all surviving patients. Questions were paralleled and asked twice. The first set reflected the function in the period six months before multimodality treatment, and the second the current function after multimodality treatment. Follow-up was at least four months, as most postoperative morbidity is reversible in this period.[16,20-22] Voiding function was measured by the following variables: bladder hypotonia, lower urinary tract symptoms (LUTS: including hesitancy, weak stream, dribbling and nocturia), urgency and incontinence. Sexual function was measured by the following variables: sexual activity, experience of pain or discomfort during intercourse, erection, ejaculation and orgasm. Quality of orgasm and erectile function were assessed using a variable analog scale (VAS). All sexual questions could also be answered by ”sexually inactive”.

Table 2. **Operative and postoperative complications**

	Locally advanced primary		**Locally recurrent**	
	No.	**(%)**	**No.**	**(%)**
Operative complications				
Bladder lesion	1	(2)	3	(5)
Ureter lesion	1	(2)	2	(3)
Urthra lesion	-		1	(2)
Immediate postoperative complications				
Voiding difficulties	21	(39)	23	(35)
Hypotonia	15	(27)	20	(30)
Chronic hypotonia	7	(13)	11	(17)
Temporalily hypotonia	8	(15)	8	(12)
Preexistent hypotonia	-		1	(2)
Urgency/ urge incontinence	6	(11)	1	(2)
Chronic hypotonia	-		1	(2)
Temporary urgency	4	(7)	-	
Preexistent urgency	2	(4)	-	
Stress incontinence	-		2	(3)
Chronic stress incontinence	-		1	(2)
Temporary stress incontinence	-		1	(2)
Urinary tract infection	10	(18)	10	(15)
Leading to sepsis	3	(5)	2	(3)
Urogenital fistula	2	(4)	6	(9)
Vesico-cutaneous fistula	1	(2)	-	
Vesico-rectal fistula	-		1	(2)
Vesico-vaginal fistula	-		1	(2)
Uretero-cutaneuos fistula	-		1	(2)
Uretero-vagina fistula	-		1	(2)
Recto-vaginal fistula	-		1	(2)
Ileum conduit fistula	1	(2)	1	(2)
Hydronephrosis	1	(2)	1	(2)
Unilateral	-		1	(2)
Bilateral	1	(2)	-	
Late postoperative complications				
Ureter fibrosis	-		2	(3)
Radiation cystitis	-		1	(2)

The response rate was 96% (76/79). Groups consisted of 37 (49%) locally advanced primary (male-female: 22-15) and 39 (51%) locally recurrent patients (male-female: 24-15). Median time between the operation and the questionnaire was 14 months (range 4 - 60 months). Patients who returned the questionnaire but who had currently or previously received an ileum conduit (n=10) were excluded for questions concerning urological dysfunction but not for sexual dysfunction. Patients indicating

”sexually inactive” (n=8) were excluded from the analysis on sexual dysfunction.

Statistical comparisons of occurrence of urogenital complications and dysfunction were performed using the T-test, Z-test, Npar-tests, Fisher’s Exact test, Wilcoxon test or McNemar test for repeated measures situations in individual persons, when appropriate. The following variables were analyzed: primary vs recurrent, sex, age (≤ 60 or > 60 years), and type of surgery (low anterior resection vs other resection types). P-values less than 0.05 were considered statistically significant.

Results

Locally advanced primary rectal cancer

The various operative and postoperative complications are summarized in Table 2. Postoperative voiding difficulties, requiring prolonged catheterizations and medication, were observed in 21 patients (39%). Fifteen of them had bladder hypotonia, which was temporarily (<4 months) in eight patients. The remaining six patients had urgency or urge incontinence, which was temporarily in four and preexistent in two.

The results of the questionnaire concerning preoperative vs current urogenital functionality are listed in Table 3. Three percent had preoperative voiding dysfunction vs 44% postoperatively (p=0.000). Bladder hypotonia requiring catheterizations (atonic bladder) was observed in 0% preoperatively vs 19% postoperatively (p=0.03). Hypotonia, not requiring catheterizations, was preoperatively observed in 3% vs 41% postoperatively (p=0.000). LUTS were observed in 6% preoperatively vs 50% postoperatively (p=0.000). Urgency was experienced by 6% preoperatively vs 58% postoperatively (p=0.000). Six percent used incontinence pads preoperatively vs 41% postoperatively (p=0.001).

Seventy-nine percent of the primary patients were sexually active preoperatively vs 32% postoperatively (p=0.000). Ninety-seven percent were able to experience orgasm preoperatively vs 53% postoperatively (p=0.000). The mean quality of orgasm, as indicated on a 5-cm analog scale, was reduced from 60% to 28% (p=0.000). Pain or discomfort during intercourse was experienced in 13% preoperatively vs 40% postoperatively (p=0.1).

The ability to have spontaneous erections was reported by 100% preoperatively vs 44% postoperatively (p=0.002). The mean quality of erectile function, as indicated on a 5-cm analog scale, had reduced from 66% to 14% (p=0.000). The ability to ejaculate had decreased from 95% preoperatively to 24% postoperatively (p=0.000).

Table 3. **Questionnaire urogenital dysfunction in locally advanced primary and locally recurrent rectal cancer.**

	Locally advanced primary rectal cancer					Locally recurrent rectal cancer				
	Preoperative		Postoperative		*p*-value	Preoperative		Postoperative		*p*-value
	n	%	n	%		n	%	n	%	
Voiding dysfunction	1/34	3	15/34	44	0.000	7/32	22	18/32	56	0.001
Hypotone bladder requiring catheterization	0/32	0	6/32	19	0.030	0/33	0	3/33	9	0.300
Hypotone bladder not-requiring catherisation	1/32	3	13/32	41	0.000	3/32	9	11/32	34	0.008
LUTS	2/34	6	17/34	50	0.000	12/32	38	25/32	78	0.001
Urgency	2/31	6	18/31	58	0.000	9/32	28	21/32	66	0.002
Incontinence	2/32	6	13/32	41	0.001	8/31	26	16/31	52	0.020
Sexual activity	27/34	79	11/34	32	0.000	23/34	68	11/34	32	0.000
Ability to have orgasm	29/30	97	16/30	53	0.000	23/32	72	10/32	31	0.000
Experience of pain/ discomfort during intercourse	2/15	13	6/15	40	0.100	1/12	8	5/12	42	0.100
Ability to achieve normal erection	18/18	100	8/18	44	0.002	15/19	79	7/19	37	0.008
Ability to ejaculate	20/21	95	5/21	24	0.000	14/20	70	2/20	10	0.000
Quality of orgasm (mean on 5-cm VAS)	3.0	60	1.4	28	0.000	2.5	50	1.1	22	0.000
Quality of erection (mean on 5-cm VAS)	3.3	66	0.7	14	0.000	2.7	54	0.5	10	0.000

Locally recurrent rectal cancer

Postoperative voiding difficulties, requiring prolonged catheterizations and medication, were observed in 23 patients (35%). Twenty of them had bladder hypotonia, which was temporarily (<4 months) in eight and preexistent in one patient. Another patient developed urge incontinence. The remaining two patients had stress incontinence, which was temporarily in one.

The questionnaire revealed that 22% of the locally recurrent patients had preoperative voiding dysfunction vs 56% postoperatively (p=0.001). Bladder hypotonia requiring catheterizations was not observed preoperatively vs 9% postoperatively (p=0.3). Bladder hypotonia, not requiring catheterisations, was preoperatively observed in 9% vs 34% postoperatively (p=0.008). LUTS were observed in 38% preoperatively vs 78% postoperatively (p=0.001). Urgency was experienced by 28% preoperatively vs 66% postoperatively (p=0.002). Twenty-six percent used incontinence pads preoperatively vs 52% postoperatively (p=0.02).

Sixty-eight percent of the locally recurrent patients were sexually active preoperatively vs 32% postoperatively (p=0.000). Seventy-two percent were able to experience orgasm preoperatively vs 31% postoperatively (p=0.000). The mean quality of orgasm, as indicated on a 5-cm analog scale, was reduced from 50% to 22% (p=0.000). Pain or discomfort during intercourse was experienced in 8% preoperatively vs 42% postoperatively (p=0.1).

The ability to get spontaneous erection was reported by 79% preoperatively vs 37% postoperatively (p=0.008). The mean quality of erectile function, as indicated on a 5-cm analog scale, had reduced from 54% to 10% (p=0.000). The ability to ejaculate had decreased from 70% preoperatively to 10% postoperatively (p=0.000).

Males vs Females (Table 4.)

The questionnaire revealed that 16% of male patients had preoperative voiding dysfunction vs 42% postoperatively (p=0.02). In female patients these figures were 7% and 61% (p=0.02). Postoperative long-term voiding dysfunction was higher in females.

Interest in sexual activity decreased in males from 80% to 37% (p=0.000) and in females from 63% to 26% (p=0.002). Both preoperative and postoperative sexual dysfunction was higher in women.

Table 4. **Questionnaire urogenital dysfunction in males and females.**

	Male					**Female**				
	Preoperative		Postoperative		*p*-value	Preoperative		Postoperative		*p*-value
	n	%	n	%		n	%	n	%	
Voiding dysfunction	6/38	16	16/38	42	0.020	2/28	7	17/28	61	0.000
Hypotone bladder requiring catheterization	0/38	0	4/38	11	0.100	0/27	0	5/27	19	0.060
Hypotone bladder not-requiring catheterization	4/36	11	13/36	36	0.040	0/28	0	11/28	39	0.010
LUTS	8/38	21	24/38	63	0.000	6/28	21	18/28	64	0.000
Urgency	4/36	11	19/36	52	0.000	7/27	26	20/27	74	0.000
Incontinence	2/36	6	9/36	25	0.040	8/27	30	20/27	74	0.000
Sexual activity	33/41	80	15/41	37	0.000	17/27	63	7/27	26	0.002
Ability to have orgasm	36/40	90	18/40	45	0.000	16/22	73	8/22	36	0.008
Experience of pain/ discomfort during intercourse	1/18	6	6/18	33	0.060	2/9	22	5/9	56	0.300
Quality of orgasm (mean on 5-cm VAS)	2.8	56	1.2	24	0.000	2.7	54	1.4	28	0.000

Multivariate analysis

Higher age (> 60 years) significantly reduced the ability to have orgasm postoperatively (p=0.046), as well as the ability to have sexual intercourse (p=0.04). Females experienced a significantly higher frequency of bladder hypotonia (p=0.02) and had a significantly increased voiding frequency to prevent incontinence in comparison with males (p=0.01). The number of patients was too small to show significant differences in urogenital morbidity between the locally advanced primary and the locally recurrent group, nor between the different types of resection.

From the 66 patients, without an ileum conduit who returned the questionnaire, 8 had voiding dysfunction preoperatively, of which 5 experienced direct postoperative voiding dysfunction. Of the remaining 58 patients, 25 developed voiding dysfunction as a new complaint, of which 13 had direct postoperative voiding dysfunction, and 33 patients developed no long-term voiding dysfunction, although 8 of them had experienced direct postoperative voiding dysfunction. Direct postoperative voiding dysfunction was found to predispose significantly for long-term voiding dysfunction (p=0.04).

Discussion

Multimodality treatment, using preoperative high dose EBRT, extended surgery and IORT, improves the outcome in both locally advanced primary and locally recurrent rectal cancer.[18,19] Cure is the main goal in these patients and treatment-related morbidity is of less importance. This is reflected by the lack of data reported on morbidity after multimodality treatment. Two reports have described general complications after IORT-containing multimodality treatment for rectal cancer,[23,24] while others briefly summarize these side effects. However, the outcome of multimodality treatment can only be placed into proper perspective if treatment-related morbidity is also taken into consideration. The probability of cure is less than the chance for urogenital morbidity.

Wound infections, neuropathy of the legs and buttocks, and urogenital morbidity are the most frequent and important treatment related sequelae. Wound infections and delayed closures resolve in time. Neuropathy is not a frequent complication after multimodality treatment, is often not severe and is in most cases self-limiting.[18,19] Urogenital morbidity, however, is a frequently observed problem in patients after multimodality treatment and is often irreversible. It is therefore more important than the literature shows and in fact may consitute a major problem.

Voiding problems according to the literature consist of difficulty to empty the bladder, hypotonia, urgency, incontinence, and urinary tract infection.[20,22,25-29] Sexual complications consist of erection and ejaculation disturbances in male patients and dyspareunia and decreased lubrication in female patients.[30]

Damage to the urogenital system can be caused by radiotherapy but more likely by surgery.[30,31] This is caused by the limited access to the lesser pelvis, the close relation of the nerves responsible for voiding and sexual function to the resection planes, and the aim of complete resection, as this is the most important prognostic oncological factor.[18,19] The incidence of urinary and sexual dysfunction rises with more radical operations.[17,31] The dissection will even be more complicated in locally recurrent rectal cancer patients, due to distortion of fascial borders and fibrotic reaction caused by previous surgery and irradiation. In some cases, the urogenital system may already be damaged. It is therefore of utmost importance to use gentle sharp dissection and to have a detailed knowledge of the pelvic and perineal anatomy. Some phases in the operation predispose for iatrogenic injury.

Most important urogenital nerves that can be harmed during the dissection are:

(1) The parasympathetic sacral splanchnic nerves (nervi erigentes), which run from the sacral nerve plexus (level S2-S4) ventrally and laterally to the inferior hypogastric plexus and from there to the bladder/ prostate, largely control micturition by controlling

the musculus detrusor vesiculae and control erection in men, may be damaged directly during dissection on the anterolateral aspect of the lower rectum anteriorly to the fascia of Denonvilliers.[1, 32-35] Partial damage will result in a decreased detrusor pressure at micturition (hypotonia) and complete denervation results in impaired bladder emptying (atonic or neurogenic bladder).
(2) The sympathetic hypogastric nerves, which run from the superior hypogastric plexus (level L3-S1) caudally and laterally (parallel with the ureters and the internal iliac vessels) to the inferior hypogastric plexus, can be damaged at the origin of the inferior mesenteric artery; or laterally to the rectum close to the middle rectal arteries at the promontory nearby the iliac vessels and around the ureter;[32,35] or when the posterior wall of the prostatic capsule is dissected.[36] Damage to the sympathetic nerves influences bladder control by a diminished proximal urethral pressure and incompetent bladder neck,[22] which results in a loss of controlling the urine when bladder pressure rises, thus resulting in increased frequency of micturition and urgency.[7] The sympathetic hypogastric nerves also control ejaculation.[37]
(3) The inferior hypogastric plexus, which contains both sympathetic pelvic splanchnic and parasympathetic hypogastric nerves, is located at the side of the lateral ligament where the visceral dorsal fascia (fascia recti) changes in the parietal dorsal fascia or fascia sacralis. This is the danger point of harming the plexus,[1,34] and therefore the lateral ligament should if possible be cut close to the mesorectum leaving pelvic plexus undamaged on the lateral pelvic wall. Whenever possible, we attempt to preserve at least one set of both nerves.
(4) The somatic pudendal nerves (deriving from S2-S4), which can delay urination by contraction of the external bladder sphincter, can suddenly compensate for increase of intraabdominal pressure (i.e., coughing) and can propel the seed by contraction of the ischiocavernous and bulbospongiosus muscles, are most vulnerable in the presacral space and ischiorectal fossa.[7]
Apart from direct injury, neuropathy of the urogenital nerves can be caused by traction on the lower rectum during mobilization, which might explain the improvement of the voiding dysfunction in many patients in the months following the operation.[34]

Postoperative urogenital dysfunction may also be caused by several non-neurogenic reasons: inflammatory changes in the perivesical tissues,[38] altered perineal anatomy,[25,28,30] immobilization, the recumbent posture, failure of perineal relaxation caused by pain, failure to open the bladder-neck due to stress induced sympathetic overactivity, bladder distension and reduced contractility as a result of high intravenous fluid loads, or bladder sedation due to residual effects of anaesthetic agents are not infrequent. These factors may explain the transient nature of symptoms encountered in many patients.[16]

External beam radiotherapy has a negative effect on the peripheral nerves, most probably as a result of damage to the capillaries of the neurovascular bundles, and may also result in a decline of smooth muscle content, diffuse fibrosis and mucosal irritation, which can cause a loss of bladder compliance, vasculogenic impotence in men, and dyspareunia in women.[30,39] Further damage can be caused by IORT, since peripheral nerves are the main dose-limiting structures for IORT.[23,40,41] The use of small radiation fields, carefully fractionated doses, exclusion of bowel and bladder, and dose titration with the time interval between initial treatment and recurrence of disease all seem necessary to prevent damage to the peripheral nerves.[42]

Postoperative urinary retention is a troublesome, though often temporarily, complication after rectal resection and is usually related to outlet obstruction.[20,43] Proper bladder drainage in the postoperative period is essential, because prolonged bladder distension will extend the problem. All patients, except those who had an ileum conduit constructed, therefore received a supra-pubic bladder catheter. This has the advantage of assessing the micturition capability, without repeated removal and placement of catheters and avoids the complication of urethral stricture. If micturition fails, pharmacological treatment may be started to improve bladder hypotonia. Long-term observation shows a declining incidence of bladder dysfunction.[17] Therefore, any indication for early postoperative surgical intervention, like a transurethral resection of the prostate in cases of urethral sphincter obstruction, hardly exists, and may, especially if the pudendal nerves are damaged, lead to incontinence.[16,44]

In this study, 36 percent (44/121) of all patients had direct postoperative voiding dysfunction requiring medical treatment, which was temporarily in more than half of them (Table 3). Long-term voiding dysfunction was significantly related to direct postoperative voiding dysfunction (p=0.04). Other reports have not identified such relation.

The questionnaire on late morbidity revealed voiding dysfunction in 31% (10/32) of the male and 58% (15/26) of the female patients, who had normal preoperative bladder function (Table 4). This was respectively 42% (14/33) after treatment of primary and 48% (12/25) after treatment of locally recurrent rectal cancer (Table 3). Other studies show a wide range voiding dysfunction rates between 7 to 73 percent, depending on radicality of resection and the attention paid on autonomous nerve preserving surgery.[4-6,8,16,17,20,25-28,30,31,37,45,46] An atonic bladder occurred between 9 to 19% in the different groups in this study, which is comparable to the reported rates ranging between 0% and 59%.[8,16,20,26-30,45] Havenga, who used a similar questionnaire for urogenital morbidity in patients after TME for primary mobile rectal cancer, revealed a postoperative voiding dysfunction ranging between 27-37%, no atonic bladder, and an incontinence rate of 5-30% in male and female groups with normal preoperative voiding function.[30] In this study, in which both sexes had a significant reduction of normal voiding function, 20% (7/34) of the males and 63% (12/19) of the females developed incontinence as a new complaint. Furthermore, females experienced a significantly higher difficulty emptying their bladder than males (p=0.02) and females deliberately urinated more frequently to prevent leakage than males (p=0.01). This may be associated with the larger bladder capacity but shorter length of the urethra in women.[30]

It is known that sexual dysfunction is a common problem after rectal resection and more frequent after larger resections.[35] After abdominosacral resection, sexual function is still normal if the S3 nerve root is severed bilaterally.[47] However, unilateral damage of S2 nerve root leads to loss of sensation in the penis or the labia and weakens erection.[33,47] After conventional operations, permanent, complete or partial erectile dysfunction is reported to occur in 5-65% of patients[8,30,46,48-51] and loss of the ability to ejaculate is reported in 12-69%.[4,8,30,46,48-51] In the study of Havenga, using a similar questionnaire to analyze sexual dysfunction after TME surgery for mobile rectal cancer, 4% of the males and 2% of the females lost the ability to achieve orgasm.[30] In this study, sexual function was also significantly influenced by the multimodality treatment. In 50% (18/36) of the male and 50% (8/16) of the female patients, and in 45% (13/29) of patients after primary and 57% (13/23) after recurrent rectal cancer treatment, the preoperative ability to have an orgasm had disappeared. The ability to achieve both erection and ejaculation was also significantly reduced in males of all groups in this study. An increase of pain or discomfort during intercourse was both observed in males and females. But the numbers were too low to draw conclusions.

Comparable to other studies,[30,46] age had a large influence on sexual activity after surgery. Higher age (> 60 years) significantly reduced the ability to have an orgasm ($p=0.046$), as well as the ability to have sexual intercourse ($p=0.04$) postoperatively. Sexual dysfunction due to autonomous nerve damage is a major problem in men after rectal surgery because of subsequent erectile and ejaculation disturbance. However, exact evaluation of sexual function in elderly men, who may find it embarrassing to discuss declining potency, is difficult. Fortunately, new pharmaceutical drugs to improve potential function have become available.

Conclusion

Multimodality treatment for locally advanced primary and locally recurrent rectal cancer can be accomplished with acceptable urogenital morbidity, weighed by the risks of uncontrolled tumorgrowth. Most urinary complications are not potentially life-threatening and become less severe in time following proper management. However, long-term voiding and sexual function is reduced in half of the patients, who had a normal function preoperatively. The main causes of voiding and sexual dysfunction after rectal surgery are most probably due to damage of the autonomic nerves supplying the urogenital organs. Completeness of the tumor resection remains the main goal of the treatment, though, sharp nerve-sparing dissection is often still possible and is essential to maintain proper urogenital function. Preoperative EBRT and IORT can have a magnifying effect on urological complications. Preoperative information to the patient about treatment related urogenital morbidity is important. Results of this study have prompted us to incorporate this information in the preoperative counselling. Furthermore, communication between the rectal surgeon and the urologist should be optimal to assess any occurring problems properly.

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Chapter 8

Summary, general conclusions and future perspectives

Summary

Chapter one gives a short introduction of the therapeutical problems in patients with locally advanced primary or locally recurrent rectal cancer, and describes how former single modality treatments can be turned into a potential curative multimodality treatment for these patients.
It discusses the aim of this study, which was to evaluate the role of IORT-containing multimodality treatment for locally advanced primary or locally recurrent rectal cancer in terms of outcome (survival, disease free survival and local control) and its associated complications and morbidity in justification of this aggressive treatment in these patients. Moreover, the technical aspects of the multimodality treatment were analysed. Finally, is lists the chapter distribution of this thesis.
Chapter two describes the results of IOERT-containing multimodality treatment in 38 patients with primary locally advanced rectal cancer without distant metastases. The 3-year overall survival, local control, and disease free survival rates of 72%, 82%, and 65% respectively, are favourable. No operative death occurred. Postoperative complications were observed in 53% of the patients and were temporarily in most patients. Wound infections were observed in 29% of the patients. Grade I neuropathy was observed 8% of the patients. The relatively high incidence of complications is considered to be acceptable in the view of the extent of the operation needed to obtain a radical tumor resection, which was achieved in 82% of the patients, and the negative impact on quality-of-life of a progressing local recurrence. Negative resection margins had a significant positive effect on outcome. Depth of tumor infiltration did not influence local control, disease free survival and survival. The presence of lymph node metastases resulted in a significantly higher distant metastases rate. Presence of preoperative pain correlated significantly with a less favorable disease free survival and metastases rate.
Chapter three compares the results of IORT-containing multimodality treatment in locally recurrent rectal cancer (n=33) with two historical control groups with the same tumor characteristics from the same centers (Catharina Hospital Eindhoven and the Daniel den Hoed Cancer Center Rotterdam). The historical controls consisted of irradiation only (n=94) or preoperative irradiation and surgery (n=19). The results of the patients treated with multimodality treatment were significantly better than those patients treated with conventional treatment modalities ($p < 0.001$). The 3-year survival rate increased from 11-14% in the historical groups up to 60% in the multimodality treatment group. Even when the possible bias of a growing surgical experience was excluded by comparing negative and positive margins between the groups, multimodality treatment appeared significantly better. Especially, those patients who have a radical tumor resection (R0-resection) seem to benefit the most from the addition of IORT.

Chapter four describes the results of IOERT-containing multimodality treatment in 37 patients with locally recurrent rectal cancer, without distant metastases. The 3-year overall survival, local control, and disease free survival rates of 58%, 60%, and 32% respectively, are promising. No operative death occurred. Postoperative complications were observed in 57% of the patients and could be treated conservatively in most cases. Wound infection was the most frequently observed complication for 22% of the patients. Neuropathy was observed in 16% of the patients. Short-term morbidity was high but was not severe and subsided spontaneously in most cases. In 20% of all patients that were alive at the moment of the analysis, the daily function was disturbed to some degree. Seventy-five percent of the patients who worked preoperatively could restart their occupation. In the light of uncontrollable locoregional disease treated with conventional treatment and the expected cure, IORT-containing multimodality treatment could be justified. Radicality (negative margins) of the resection was an important factor in outcome, significantly associated with improved survival, local control and disease free survival. Re-irradiation is preferred in previously irradiated patients. Preoperative symptoms of pain predisposed for a significantly worse prognosis and a significantly higher rate of macroscopically positive resection margins.

Chapter five reports on the surgical technique and results of the abdominosacral approach as part of the multimodality treatment in 50 patients. It is a valuable technique for radical resection of rectal cancers with involvement of the dorso-lateral pelvic walls or the sacrum. It provides a wide access resulting in a good visualization of the dissection, enables en bloc resection of the sacrum and pelvic floor muscles, and is well tolerated with acceptable morbidity and mortality. It is performed in a two stage procedure, in which the patient is turned from supine after the abdominal approach to prone position to perform the transsacral approach of the resection. The operation time ranged from 210 to 590 minutes (median 390 min.), and blood loss ranged from 400 to 10,000 ml (median 3,500 ml). No operative or hospital deaths occurred. Although the abdominosacral resection results in a high rate of postoperative complications (82%), predominantly due to (perineal) wound infections (48%), long-term morbidity is acceptable. Radical tumor resection was achieved in 52% of the patients. The 3-year overall survival, disease free survival and local control rates were, respectively, 41%, 31%, and 61%. Radicality of the resection was a significant factor influencing survival, disease free survival and local control.

Chapter six describes the anesthetic management and perioperative results of 106 patients receiving multimodality treatment for rectal cancer. During this extensive operation the anesthesiologist is faced with major problems such as: massive transfusion requirements, hypothermia, intraoperative position changes, the need to transport the patient to the IOERT-applicator, and the risk associated with remote monitoring of the patient during the ten minutes of the IOERT application. The average duration of anesthesia was 6 hours (range 3-10½ hrs) and the mean blood loss was 3 liters (range 0.4-14 L). The cardiac index, blood pressure, heart rate,

blood gasses and electrolytes of the patients were kept within acceptable ranges. Recovery of the patients from anesthesia was satisfactory. Two patients died due to postoperative hemorrhage in the ICU after 34 and 48 days. Seven patients died after being discharged as a result of treatment induced morbidity (51-205 days postoperatively). With adequate pre-operative assessment and optimalization of the patients' condition, maintaining peroperative hemodynamic stability by immediate resuscitation with warm fluids and blood products with the help of adequate monitoring and multidisciplinary communication, anesthetic complications could be minimized. The concern of many surgeons, anesthesiologists and other supporting team members about radiation exposure and dangers of remote monitoring does not seem to be justified.
Chapter seven analyses the urological and sexual complications and morbidity as part of an IORT-containing multimodality treatment in 121 patients with locally advanced primary or locally recurrent rectal cancer. Operative urologic complications were observed in 8 patients (7%) and consisted of bladder lesions (n=4), ureter lesions (n=3) and one urethra tear. Postoperatively, voiding difficulties requiring prolonged catherisation and/or medication were observed in 37% of the patients (n=45), of which 5 (11%) were preexistent and 20 (44%) temporary. Fistulas of the bladder were observed in three patients, fistulas of the ureter in four patients, and another patient developed a recto-vaginal fistula. Late urogenital morbidity was analysed by a questionnaire, which was returned by 76 patients (96%) (37 primary locally advanced and 39 locally recurrent patients) with a minimal follow-up of 4 months. Identical questions were asked reflecting both the current function, following the treatment, and the function six months prior to the treatment. The questionnaire revealed identifiable voiding dysfunction as a new problem in 31% of the male and 58% of the female patients. This dysfunction occured in 42% patients after locally advanced primary treatment and in 48% of the patients after locally recurrent rectal cancer treatment. The preoperatively present ability to have an orgasm had disappeared in 50% of the male and female patients. In 45% of the patients this ability disappeared after locally advanced primary treatment and in 57% of the patients after locally recurrent rectal cancer treatment. The operative urological complication rate is low and most postoperative complications are not life-threatening. Surgery for these cancers requires extended circumferential margin excision (ECME), which may jeopardize the urogenital nerves.

General conclusions and future perspectives

The introduction of IORT-containing multimodality treatment for locally advanced rectal cancer in the Catharina Hospital in Eindhoven and the Daniel den Hoed Cancer Center in Rotterdam has led to improved local control and survival compared to historical controls.

Introduction of IORT-containing multimodality treatment for locally recurrent rectal cancer has changed the treatment from merely palliative to a possible curative treatment. Two elements of the multimodality treatment appeared to be crucial for a favourable outcome: firstly, increase of the therapeutic ratio of the radiotherapy by combining preoperative radiotherapy with an intraoperative boost, and secondly, optimalization of surgery aiming at radical resection (negative margins). Growth extending to or beyond the rectal compartment (fascia propria) in primary locally advanced rectal cancer and the absence of the fascia propria recti and the subsequent enlargement of the tumor compartment in locally recurrent rectal cancer are the anatomical basis for the this multimodality treatment.
The willingness of referring surgeons and radiotherapists to centralize the treatment of patients with primary locally advanced and locally recurrent rectal cancer was a prerequisite to develop this approach. The importance of centralization of these patients is demonstrated by the fact that increasing experience has led to the decrease of positive tumor resection margins. The results in this study show that IORT-containing multimodality treatment seems to improve the outcome at the cost of an acceptable long-term morbidity. Appropriate selection of patients, based on tumor characteristics and imaging, for multimodality treatment is crucial to avoid unnecessary morbidity. In all separate studies, radical tumor resection was identified as a crucial significant positive factor influencing outcome.

Although the results in this retrospective study as well as in other IORT-containing multimodality treatment studies show improved oncological results in comparison to more conventional treatments, the benefit of addition of IORT has never been proven by a prospective randomized trial. As the use of IORT-containing multimodality treatment is increasing throughout the world, such action should be undertaken. A prerequisite for such study is the design of an adequate staging system for both primary locally advanced and locally recurrent rectal cancer. The fact that only a few centers have IORT facilities influences its accessibility. However, introduction of mobile linear accelerators for IOERT delivery will overcome this problem. As a result of introduction of TME-surgery for mobile rectal cancer, the amount of patients with a local recurrence will decline, however, an eventual local recurrence would be more troublesome to treat. Therefore, more attention will be focused on locally advanced primary rectal cancer.

The challenge for the future is the fine-tuning of this treatment. Selection of patients can be improved by better staging for distant metastatic disease. The role of Positron Emission Tomography (PET) in differentiating scar tissue from recurrent colorectal cancer is well established and is therefore important in the early detection of a local recurrence, and, additionally, PET may guide other imaging techniques for better staging of metastases, which has a cost-effective effect on clinical management as surgery may be avoided in patients with distant metastases.[1,2] On the other hand, efforts have to be directed toward mechanisms that improve safety of the total dose of irradiation and the resectablity rate.

Improvement of local staging by helical CT or high resolution MR, in the future combined with PET imaging, will enable to predict which margins are threatened.[2-4] These images will improve guidance of preoperative irradiation and surgical strategy, which can increase the number of radical tumor resections. Other mechanisms include addition of chemotherapy to the preoperative radiotherapy, which may further increase the radiotherapeutic ratio due to its radiation sensitization effect. Introduction of radiochemotherapy may contribute to more radical tumor resections.[5,6,7] Radio-Immuno Guided Surgery (RIGS) can be of help for the identification of the area at risk, which has to be boosted by IORT and can reduce the sampling error of frozen sections.[8,9] Furthermore, the role of hypoxic cell sensitizers during IORT, to increase its radiotherapeutic effect, will be investigated.[10] Finally, now that local tumor control seems to be achieved in a large number of these patients, efforts have to be directed to reduce the high distant metastases rate, occurring in more than 50% of the patients. Future protocols of concomitant radiochemotherapy and maintenance adjuvant chemotherapy will address the treatment of possible systemic disease.

Centralization of the treatment of patients with locally advanced primary and locally recurrent rectal cancer in centers with expertise should be mandatory.

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Samenvatting, algemene conclusies en toekomst

Samenvatting

Hoofdstuk één bevat een korte introductie over de therapeutische problemen bij patiënten met een primair lokaal voortgeschreden dan wel een lokaal recidief rectumcarcinoom en beschrijft hoe uit conventionele behandelingen een potentieel curatieve multimodale behandelingsstrategie is ontwikkeld.
Het doel van de studie, namelijk de evaluatie van de rol van IORT-bevattende multimodale behandeling voor primair lokaal voortgeschreden dan wel lokaal recidief rectumcarcinoom, wordt beschreven in termen van oncologisch resultaat van de behandeling (overleving, ziekte-vrije-overleving en lokale controle) en de daarmee geassocieerde complicaties en morbiditeit om zodoende tot een rechtvaardiging van deze aggressieve behandeling te komen. Daarnaast worden de technische aspecten van de multimodale behandeling geanalyseerd
Vervolgens worden de hoofdstukken van de onderhavige thesis besproken.
Hoofdstuk twee beschrijft de resultaten van de IORT-bevattende multimodale behandeling bij 38 patiënten met primair lokaal voortgeschreden rectumcarcinoom zonder afstandsmetastasen. De 3-jaars overleving, lokale controle en ziekte-vrije-overleving van respectievelijk 72%, 82% en 65% van deze patiënten zijn gunstig te noemen. Geen van de patiënten overleed tijdens de operatie. Postoperatieve complicaties werden waargenomen bij 53% van de patiënten en waren veelal tijdelijke van aard. Wondinfecties werden geconstateerd bij 29% van de patiënten. Graad I neuropathie werd waargenomen bij 8% van de patiënten. De relatief hoge incidentie van complicaties is acceptabel te noemen gezien de uitgebreidheid van de operatie, welke nodig is om een microscopisch radicale resectie te bewerkstelligen, en het negatieve effect dat lokale tumorprogressie zou hebben op de kwaliteit van leven, indien geen adequate behandeling zou plaatsvinden. Een radicale resectie werd verkregen werd bij 82% van de patiënten. Resectie met microscopisch radicale marges had een significant positieve invloed op de oncologische prognose. Mate van tumorinfiltratie bleek geen invloed te hebben op de lokale controle, ziekte-vrije-overleving en overleving. Aanwezigheid van positieve lymfklieren had een significante invloed op het ontstaan van afstandsmetastasen. Preoperatief aanwezige pijnklachten waren significant gecorreleerd met een slechtere ziekte-vrije-overleving en met een significant hogere kans op afstandsmetastasering.
Hoofdstuk drie vergelijkt de resultaten van IORT-bevattende multimodale behandeling bij het lokaal recidief rectumcarcinoom (n=33) met twee historische controlegroepen, die dezelfde tumorkarakteristieken vertoonden en uit dezelfde centra afkomstig waren (Catharina ziekenhuis Eindhoven en de Daniel den Hoed kliniek Rotterdam). De historische controlegroepen bestonden uit een patiëntengroep, behandeld met bestraling alleen (n=94), en een, behandeld met preoperatieve bestraling in combinatie met chirurgie (n=19).

De resultaten van de patiënten, behandeld met multimodale therapie, waren significant beter dan die van de historische controlegroepen ($p < 0.001$). De 3-jaars overlevingscijfers waren 11% en 14% bij de twee historische controlegroepen tegen 60% bij de multimodale behandelingsgroep. Zelfs als de verbeterde chirurgie als bias werd weggenomen, door vergelijking te maken tussen subgroepen van radicale en irradicale resectiemarges, bleek multimodale behandeling significant beter. Vooral patiënten, bij wie een radicale tumorresectie (R0-resectie) mogelijk was, lijken het meeste gebaat met toevoeging van IORT.
Hoofdstuk vier beschrijft de resultaten van een IOERT-bevattende multimodale behandeling bij 37 patiënten met lokaal recidief rectumcarcinoom zonder afstandsmetastasen. De 3-jaars overleving, lokale controle en ziekte-vrije-overleving van respectievelijk 58%, 60% en 32% van deze patiënten zijn gunstig te noemen. Geen van de patiënten overleed tijdens de operatie. Postoperatieve complicaties werden waargenomen bij 57% van de patiënten en konden in de meeste gevallen conservatief behandeld worden. Wondinfecties, bij 22% van de patiënten, waren de meest frequent waargenomen complicaties. Neuropathie werd bij 16% van de patiënten gediagnostiseerd. De morbiditeit op de korte termijn was hoog, maar veelal niet ernstig en tijdelijk van aard. Bij 20% van de patiënten, die in leven waren op het moment van de analyse, was het dagelijks functioneren gestoord. Vijfenzeventig procent van de patiënten, die voor de operatie een baan hadden, konden deze na de operatie weer oppakken. De morbiditeit van ongecontroleerde loco-regionale tumorgroei na conventionele behandeling en de kans op curatie rechtvaardigen de multimodale aanpak. Radicaliteit (negatieve marges) van de resectie bleek een belangrijke, significant positieve factor voor de overleving, lokale controle en ziekte-vrije-overleving. Bij reeds bestraalde patiënten verdient herbestraling de voorkeur. Preoperatieve radiotherapie was beter dan geen preoperatieve radiotherapie bij reeds bestraalde patiënten. Patiënten met preoperatieve pijnklachten hadden een significant slechtere prognose en waren significant vaker geassocieerd met irradicale resecties.
Hoofdstuk vijf beschrijft de chirurgische techniek en de resultaten van de abdominosacrale resectie als onderdeel van de multimodale behandeling bij 50 patiënten. Het is een waardevolle chirurgische techniek bij het streven naar een radicale resectie bij rectale carcinomen met infiltratie in de dorsolaterale bekkenwand of het sacrum. Het geeft een wijde toegang, hetgeen resulteert in een uitstekende visualisatie, maakt en bloc resectie van het sacrum en de bekkenbodemspieren mogelijk, en wordt goed getolereerd met een acceptabele morbiditeit en mortaliteit. De procedure bestaat uit twee fasen, waarin de patiënt gedraaid wordt van rugligging voor de abdominale fase en naar buikligging voor de sacrale fase. De operatietijd wisselde van 210 tot 590 minuten (mediaan 390 min.) en het bloedverlies bedroeg mediaan 3.5 liter (spreiding 0.4-10 L). Er was geen perioperatieve sterfte. Hoewel de abdominosacrale resectie gepaard gaat met een hoog percentage postoperatieve complicaties (82%), m.n. bestaande uit (perineale) wondinfecties (48%), is de morbiditeit op de lange termijn acceptabel. Radicale

tumorresectie werd verkregen bij 52% van de patiënten. De 3-jaars overleving, ziekte-vrije-overleving en lokale controle waren respectievelijk 41%, 31% en 61%. Radicaliteit van de resectie was een significant positieve factor voor de overleving, ziekte-vrije-overleving en lokale controle.

Hoofdstuk zes beschrijft de anesthesie en de perioperatieve resultaten van 106 patiënten, die behandeld werden met multimodale behandeling voor een rectumcarcinoom. Gedurende deze operatieve procedure wordt de anesthesist geconfronteerd met een aantal belangrijke problemen zoals: massale bloedtransfusiebehoefte, hypothermie, intraoperatieve wisseling van ligging en transport van de patiënt naar de lineaire versneller, en de risico's van bewaken van de patiënt op afstand gedurende de tien minuten van IOERT applicatie. De gemiddelde anesthesieduur bedroeg 6 uur (spreiding 3-10½ uur) en het gemiddelde bloedverlies was 3 liter (spreiding 0.4-14 liter). De cardiac index, bloeddruk, polsfrequentie, bloedgassen en electrolyten van de patiënten bleven alle binnen acceptabele grenzen. Herstel van de patiënten van de anesthesie was ongecompliceerd. Twee patiënten stierven ten gevolge van postoperatieve bloedingen op de IC na 34 en 48 dagen. Zeven patiënten stierven na hun ontslag uit het ziekenhuis door behandelingsgerelateerde complicaties (51-205 dagen postoperatief). Dankzij adequate preoperatieve screening en optimalisatie van de conditie van de patiënt en dankzij behoud van peroperatieve hemodynamische stabiliteit door aggressieve resuscitatie met warme vloeistoffen en bloedproducten, alerte bewaking en multidisciplinaire communicatie, konden anesthesiologische complicaties worden geminimaliseerd. De bezorgdheid van vele chirurgen, anesthesisten en leden van de ondersteunend team over het stralingsgevaar en het bewaken van de patiënt op afstand, is niet gerechtvaardigd.

Hoofdstuk zeven beschrijft de urologische en sexuele complicaties en de morbiditeit als gevolg van IORT-bevattende multimodale behandeling bij 121 patiënten met een primair lokaal voortgeschreden dan wel lokaal recidief rectumcarcinoom. Operatieve urologische complicaties werden waargenomen bij 8 patiënten (7%) en bestonden uit blaasletsels (n=4), ureterletsels (n=3) en één urethraletsel. Postoperatieve mictieproblemen, die langdurigere catherisatie nodig maakten en/ of leidden tot het voorschrijven van medicatie, werden waargenomen bij 37% van de patiënten (n=45), van wie 5 (11%) reeds preexistente klachten hadden en van wie 20 (44%) slechts tijdelijk klachten hadden. Fistels van de blaas ontstonden bij drie en van de ureter bij vier patiënten. Een andere patiënt ontwikkelde een rectovaginale fistel. Late urogenitale morbiditeit werd geëvalueerd met een enquête, die door 76 (96%) geretourneerd werd (37 primair lokaal voortgeschreden en 39 lokaal recidief patiënten) van de 79 nog in leven zijnde patiënten met een minimale follow-up van 4 maanden. Dezelfde vragen betreffende urogenitale functionaliteit werden gesteld over de periode van 6 maanden voorafgaande aan de multimodale behandeling en over de periode na de behandeling. Uit de enquête bleek dat mictiestoornissen als een nieuwe klacht zich openbaarden bij 31% van de mannelijke en bij 58% van de vrouwelijke patiënten, en bij 42% van de patiënten met primair lokaal

voortgeschreden en bij 48% met recidief rectumcarcinoom. Het voor de operatie aanwezige vermogen om een orgasme te krijgen verdween bij 50% van de mannelijke en bij 50% van de vrouwelijke patiënten. Dit was ook het geval bij 45% van de patiënten na behandeling van een primair lokaal voortgeschreden en 57% na behandeling van een recidief rectumcarcinoom.
Het aantal operatieve en postoperatieve complicaties na multimodale behandeling is relatief laag en de meeste complicaties zijn niet levensbedreigend. Chirurgie voor deze tumoren vereist uitgebreide resectie van de circumferentiele marge (ECME), waardoor de urogenitale zenuwen gevaar lopen.

Algemene conclusies en toekomst

De introductie van IORT-bevattende multimodale behandeling voor het primair lokaal voortgeschreden rectumcarcinoom in het Catharina Ziekenhuis te Eindhoven en de Daniel den Hoed Kliniek te Rotterdam hebben geleid tot een verbeterde lokale controle en overleving, vergeleken met historische controle groepen.
Introductie van IORT-bevattende multimodale behandeling voor het lokaal recidief rectumcarcinoom heeft de therapie veranderd van een met name palliatieve naar een meer curatieve therapie. Twee elementen van de multimodale behandeling waren cruciaal voor de ontwikkeling van deze verbeterde therapie; allereerst: verhoging van de therapeutische ratio van de radiotherapie door combinatie van preoperatieve radiotherapie met een intraoperatieve boost, en ten tweede: optimalisatie van de chirurgie met als doel een microscopisch radicale resectie te bewerkstelligen. Tumorgroei tot aan of buiten het rectale compartiment (fascia propria) bij primair lokaal voortgeschreden rectumcarcinoom en de afwezigheid van de fascia propria recti, en dientengevolge vergroting van het tumorcompartiment bij lokaal recidief rectumcarcinoom, vormen de anatomische basis voor deze multimodale behandeling.
De bereidheid van chirurgen en radiotherapeuten om de patiënten met een primair lokaal voortgeschreden en lokaal recidief rectumcarcinoom te verwijzen, was een voorwaarde voor de ontwikkeling van deze multimodale behandeling. Het belang van gecentraliseerde behandeling van deze patiëntengroepen blijkt uit het feit dat de toegenomen expertise geleid heeft tot een afname van het aantal irradicale resecties. De resultaten in deze studie doen vermoeden dat IORT-bevattende multimodale behandeling het oncologisch resultaat verbetert ten koste van een acceptabele lange-termijn morbiditeit. Adequate selectie van patiënten voor multimodale behandeling, welke selectie gebaseerd is op tumorkarakteristieken en beeldvormende diagnostiek, is cruciaal om onnodige morbiditeit te voorkomen. In alle deelonderzoeken bleek dat radicale tumorresectie een significant positieve invloed had op het oncologische resultaat.

Hoewel de resultaten in deze retrospectieve studie, alsmede in andere studies naar het effect van IORT-bevattende multimodale behandeling, een verbeterde oncologische prognose te zien geven, vergeleken met andere conventionele behandelingen, is de waarde van toevoeging van IORT nog nooit bewezen door middel van een prospectief gerandomiseerde studie. Aangezien het gebruik van IORT-bevattende multimodale behandeling in de wereld toeneemt, zou een dergelijke studie eigenlijk uitgevoerd dienen te worden. Een voorwaarde voor een dergelijke studie is de ontwikkeling van een adequaat stageringssysteem voor zowel het primair lokaal voortgeschreden als voor het lokaal recidief rectumcarcinoom. Het feit dat alleen een paar centra de beschikking hebben over IORT faciliteiten beinvloedt de toegankelijkheid ervan. Introductie van mobiele lineaire versnellers voor IORT applicatie zal dit probleem wellicht verminderen. Ten gevolge van de introductie van TME-chirurgie voor het mobiele rectumcarcinoom zal het aantal patiënten, dat een lokaal recidief krijgt, in de toekomst afnemen. Daarentegen zal, wanneer een lokaal recidief optreedt, dit moeilijker te behandelen zijn. Daarnaast zal meer aandacht uitgaan naar de behandeling van patiënten met een primair lokaal voortgeschreden rectumcarcinoom om het aantal lokaal recidieven in deze risicogroep verder te verminderen.

De uitdaging voor de toekomst is de verfijnde afstelling van deze behandeling. Selectie van patiënten kan worden verbeterd door betere detectie van afstandsmetastasen. Positron Emissie Tomografie (PET) kan differentiëren tussen littekenweefsel en een lokaal recidief, is belangrijk bij de vroege detectie van het lokaal recidief en kan andere beeldvormende diagnostiek aansturen bij detectie van afstandsmetastasen.[1,2] In het geval afstandsmetastasen worden aangetoond is dit kosten-effectief voor het klinisch management, omdat dan van chirurgie kan worden afgezien.[2] Anderzijds is een verbetering van mechanismen gewenst om de veiligheid van totale bestralingsdosis te vergroten en de resectabiliteit te verhogen. Verbetering van de lokale stagering met spiraal CT en hoge resolutie MRI, in de toekomst in combinatie met PET-scan, zullen de behandelaar vooraf kunnen verduidelijken welke chirurgische resectievlakken bedreigd zijn.[2-4] Deze diagnostische beelden zullen de bepaling van het preoperatieve bestralingsveld alsmede de bepaling van de chirurgische strategie verbeteren, hetgeen op zijn beurt weer zal leiden tot een toename van het aantal radicale tumorresecties. Een ander mechanisme is de toevoeging van chemotherapie aan de preoperatieve radiotherapie als bestralings-sensitizer, waardoor de radiotherapeutische ratio verder verhoogd wordt. Invoering van radiochemotherapie zal mogelijk bijdragen tot meer radicale tumorresecties.[5,6,7] Radio-Immuno Guided Surgery (RIGS) zou behulpzaam kunnen zijn bij de identificatie van de risicogebieden, die een IORT boost dienen te krijgen, en zou het aantal fout-negatieve vriescoupes mogelijk verminderen.[8,9] Daarnaast zal de rol van hypoxische cel sensitizers gedurende de IORT om het radiotherapeutische effect te vergroten onderzocht gaan worden.[10] Waar lokale tumorcontrole bij een groot aantal van deze patiënten inmiddels lijkt te zijn bewerkstelligd, verdient thans de reductie van het hoge aantal afstandsmetastasen, die zich nu bij meer dan 50%

van de patiënten voordoen, alle aandacht. Toekomstige onderzoeksprotocollen betreffende preoperatieve radiochemotherapie en postoperatieve adjuvante chemotherapie, zullen dit probleem gaan aanpakken.
Centralisatie van de behandeling van patiënten met primair lokaal voortgeschreden dan wel lokaal recidief rectumcarcinoom bij centra met expertise, lijkt aangewezen.

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APPENDIX

TNM classification and stage grouping for colon and rectum Abbreviations
TNM UICC 1987, staging classification of Colorectal Cancer

Primairy Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of tumor in resected specimen (prior polypectomy or fulgeration)
Tis	Carcinoma in situ
T1	Invades submucosa
T2	Invased muscularis propria
T3/T4	Depends on wheter serosa is present

- Serosa is present:
  - T3 Invades through muscularis propria into
    Subserosa Serosa (but not trhough)
    Pericolic fat within the leaves of the mesentery
  - T4 Invades through serosa into free peritoneal cavity or through serosa into contiguous organ

- No serosa (distal two thirds rectum, posterior left or right colon)
  - T3 Invades through muscularis propria
  - T4 Invades through the proper fascia into other organs (vagina, uterus, prostate, ureter, bladder, small bowel)

Regional Lymph Nodes (N)

NX	Nodes cannot be assessed (e.g. local excision only)
N0	No regional node metastasis
N1	1-3 positive nodes
N2	4 or more positive nodes
(N3	Central nodes positive)

Distant Metastases (M)

MX	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases present

Abbreviations

TME	Total Mesorectal Excision
R0-resection	Resection with microscopical negative margins
R1-resection	Resection with microscopical positive margins
R2-resection	Resection with macroscopical positive margins
EBRT	External Beam RadioTherapy
IORT	IntraOperative RadioTherapy
IOERT	IntraOperative Electron beam RadioTherapy
IOHDR	IntraOperative High Dose Rate brachytherapy
ECME	Extended Circumferential Margin Excision
RIGS	Radio-Immuno Guided Surgery
PET	Positron Emission Tomography

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CURRICULUM VITAE

Guido Mannaerts was born on December 21th, 1964 in Tilburg, the Netherlands. He graduated high school in Amsterdam, De Nieuwe School (Atheneum B) in 1985. He attended Medical School at the State University of Amsterdam and graduated in 1993. Within this period he received the first year certificate (propedeuse) in economics. From 1993 to 1994 he worked as a research assistant for the development of trauma-registration systems at the Free university of Amsterdam (Head: Prof Dr. H. Haarman). From 1994 to 1995 he worked as a surgical resident at the Onze Lieve Vrouwe Gasthuis Amsterdam (Head: Dr H. Hoitsma). In June 1996 he started his surgical training in the Catharina Ziekenhuis Eindhoven (Head: Dr J. Jakimowicz). In July 2000 he continued his surgical training in the University Hospital Maastricht (Head: Prof. Dr. M.J.H.M. Jacobs). In July 2001, he will return for his last year of surgical residency to the Catharina Ziekenhuis to specialize in surgical gastroenterology and surgical oncology.
He is married to Katinka Reijnders, and they have a son Eric and a daughter Juliëtte.

Achterzijde boekje

The authors of this thesis, Guido Mannaerts, was born on 21th of December 1964 in Tilburg, the Netherlands. He attended Medical School at the State University of Amsterdam. In 1993 he worked as a research assistant for the development of trauma-registration systems at the Free university of Amsterdam. In 1994 he worked as a surgical resident at the Onze Lieve Vrouwe Gasthuis Amsterdam. In 1996 he started his training in general surgery in the Catharina Ziekenhuis Eindhoven. In 2000 he continued his surgical training in the University Hospital Maastricht. In 2001, he will return for his last year of surgical residency to the Catharina Ziekenhuis to specialize in GE/ Oncology.

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STELLINGEN

Behorende bij het proefschrift ”IORT-containing multimodality treatment for locally advanced primary and locally recurrent rectal cancer”.

G.H.H. Mannaerts, Groningen, 6 juni mei 2001

1. A local recurrence is a surgical complication that can be almost completely eliminated. Heald RJ. The ‘Holy plane’ of rectal surgery. J R Soc Med 1988; 81: 503-8.

2. Het verrichten van een microscopisch radicale resectie is de belangrijkste positieve prognostische factor bij de multimodale behandeling van een lokaal voortgeschreden en een lokaal recidief rectumcarcinoom.

3. Een lokaal recidief rectumcarcinoom is, door het ontbreken van de fascia propria, per definitie vergroeid met de omgeving.

4. De bereidheid van chirurgen en radiotherapeuten om de behandeling van patiënten met een lokaal voortgeschreden of een lokaal recidief rectumcarcinoom gecentraliseerd te doen plaats vinden, was een vereiste voor de ontwikkeling van deze in opzet curatieve multimodale behandeling.

5. Het opereren van een lokaal recidief rectumcarcinoom in een daarvoor niet geschikte setting leidt vrijwel zeker tot een irradicale resectie met een nog lastiger te behandelen lokaal re-recidief in het vooruitzicht.

6. Indien bij een operatie voor een rectum- dan wel rectosigmoïdcarcinoom een lokaal voortgeschreden tumor (gefixeerd aan de omgeving) wordt aangetroffen, doet men er verstandig aan geen poging tot resectie te ondernemen. Het verdient dan de aanbeveling om de craniale zijde van de tumor met clips te markeren, een eindstandig colostoma aan te leggen en een spacer, bij voorkeur sigmoid of omentum, in het kleine bekken te situeren, zodat daarna hoge dosis radio(chemo)therapie kan worden toegepast, alvorens tot resectie over te gaan.

7. Met name microscopisch radicale resecties van lokaal recidief rectumcarcinomen lijken het meeste gebaat bij toevoeging van IORT.

8. Toevoeging van ”radiation sensitizers” zal het downstaging en downsizing effect van preoperatieve radiotherapie vergroten en daarmee de lokale tumorcontrole alsmede de curatie verbeteren.

9. In het kader van de vroege diagnostiek van colorectale maligniteiten zouden in alle toiletten de diepspoelpotten vervangen dienen te worden door vlakspoelpotten.

10. In de opzet van een geïntegreerd ziekenhuisregistratiesysteem, dient het contact tussen patiënt en arts centraal te staan, omdat vanuit dit contact de acties ontstaan die elk proces in een ziekenhuis initiëren, hetgeen voor geen enkel ander soortig contact in het ziekenhuis geldt.

11. Het beoogde effect van de invoering van het arbeidstijdenbesluit in de gezondheidszorg wordt deels teniet gedaan door de registratie daarvan.

12. We leven in een wereld, waarin de bereikbaarheid toeneemt, maar de beschikbaarheid afneemt.

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